University of Alberta

New Methods and Strategies for the Preparation and Synthetic Applications of Organoboronates

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment

of the

requirements for the degree of Doctor of Philosophy

Department of Chemistry

Edmonton, Alberta

Spring 2004

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Abstract

The synthesis and use of boronic acids play a central role in modern organic chemistry. Despite a significant amount of work in this area, free boronic acids are still relatively difficult to synthesize and purify. A solid phase strategy for the synthesis and purification of boronic acids is presented in Chapter 2. This strategy relies on the use of DEAM-PS resin as an efficient support to immobilize and derivatize arylboronic acids. Using this solid support, a wide range of boronic acids can be accessed through nucleophilic substitution, reductive amination, amide coupling, urea, thiourea, and anilide formation, as well as Ugi four-component coupling.

The use of diisopinocampheylborane for the synthesis of *E*-alkenylboronic acids is presented in Chapter 3. Hydroboration with this easily accessible reagent, followed by oxidation with acetaldehyde, hydrolysis, and trituration in hexanes generates *E*-alkenylboronic acids of very high purity. The products made available by this method are useful precursors for cycloaddition reactions of alkenylboronates, among other applications.

Chapter 4 describes a resin-to-resin Suzuki coupling methodology. This strategy allows for the convergent synthesis of biphenyl compounds, some of which would be difficult to make via a traditional linear approach. A small parallel library of biphenyl

compounds was made using an automated synthesizer, illustrating the usefulness of a resin-to-resin strategy in combinatorial chemistry.

The development of a method for the asymmetric addition of allylboronates to aldehydes under Lewis acid catalysis is presented in Chapter 5. Using camphor-derived allylboronates, this method has several advantages over existing methodologies. Significantly, it combines important features such as stability of the reagents, wide substrate scope, and very high diastereo- and enantioselectivity. On a practical level, it proves to be useful for the stereoselective synthesis of gram quantities of homoallylic alcohols.

Finally, Chapter 6 presents our efforts in the area of cycloaddition reactions using alkenylboronic acid-diethanolamine adducts. Despite the disappointing results, this study underlines the importance of having easy access to free boronic acids in their pure form. In this regard, it provides an interesting link with the research described in Chapters 2 and 3.

Acknowledgements

Although this thesis represents a good part of my work accomplished over the past five years, it is also a reflection of constant team effort. No scientific work can be executed without the help and support of a great number of people.

First, I would like to thank my supervisor Professor Dennis G. Hall for his invaluable help and guidance throughout my graduate studies. Starting as a summer student in his laboratory, he has always been cheerful and optimistic with our research projects, both in good times and bad times (Never give up!). I am also grateful for the freedom he has given me towards my research, by encouraging me to explore ideas of my own. Over the years, he has also succeeded in creating a very stimulating learning environment. The format of the group meetings, which include seminars and problem sets, the encouragement to read the current literature through a journal club, and the generosity he has shown by sending us to various conferences all help the students to keep learning beyond the classroom.

I would also like to thank all the Hall group members, past and present, for their support and stimulating discussions over the years. More specifically, I am greatly indebted to Jyoti Tailor, Christian Bérubé, Mark Zak, Kim Thompson, Barry Touré, Leyla Asadi, Hugo Lachance, and Xiaosong Lu who have collaborated with me on various aspects of my research.

Special thanks go to Jason Kennedy, Duane Stones, and Hugo Lachance for proofreading this thesis. As far as proofreading goes, they have done a terrific job by giving me a lot of useful advice.

Any scientific endeavour could not meet its objectives if it was not for the research support staff. In this regard, researchers in the Department of Chemistry are lucky to count on the expertise of a number of very efficient people. Everyone in the X-

Ray Crystallography lab, the Mass Spectrometry lab, the Spectral Services labs, the micro-analytical lab, the NMR labs, the glass shop, the machine shop, and the storeroom has made my stay easier and more agreeable. More specifically, I would like to thank Dr. Angie Morales-Izquierdo, and Dr. Robert McDonald without whom some important data would not appear in this thesis.

I would also like to thank the office staff of the Department, especially Diane Dowhaniuk, without whom many deadlines would have been missed.

The experience of being a graduate student would be incomplete without the possibility to teach our knowledge to other students. In this respect, I would like to thank Dr. Lois Browne for her hard work at organizing the undergraduate labs, and for instilling great confidence in our teaching abilities.

Of course, none of the contents of this thesis would have been possible without the help of funding agencies. I am very grateful to the Natural Sciences and Engineering Research Council (NSERC) of Canada, the Alberta Heritage Foundation for Medical Reasearch (AHFMR), and the University of Alberta for supporting me financially throughout my graduate studies.

Finalement, j'aimerais remercier tous ceux qui ont rendu cette aventure possible par d'autres moyens. Merci à mes parents Jean-Paul et Louise qui ont toujours fortement soutenu mes études. Merci aux autres membres de ma famille (Martin, Richère, Ann-Sophie, Laurence, Cécile, Margot, ma marraine Louise, etc.) pour leur soutien et leur chaleur lors de mes séjours au Québec. Thanks to all my friends, without whom life wouldn't be worth it. Finally, thanks to Darcie and my future family, who have provided me with great support towards the end of my graduate studies.

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LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
AM-PS	Aminomethyl-Polystyrene
Anal.	Elemental Analysis
approx.	approximately
APT	attached proton test
Ar	Aryl
BB	broad band
Bn	Benzyl
BNCT	boron neutron capture therapy
br s	broad singlet
Bu	Butyl
ca.	circa
Calcd	Calculated
Cy	Cyclohexyl
d	doublet
dba	dibenzylideneacetone
de	diastereomeric excess
dec.	decomposition
DEAM-PS	Diethanolaminomethyl-Polystyrene
DIBAL-H	Di-*i*-butylaluminum hydride
DIC	Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EI	Electron Impact
equiv.	equivalents

er	enantiomeric ratio
ES	Electrospray
Et	Ethyl
FTIR	Fourier-Transform Infrared
FW	Formula Weight
h	hour/hours
HOBt	1-Hydroxybenzotriazole
HBTU	*O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Ipc	Isopinocampheyl
IR	Infrared
m	multiplet
Me	Methyl
min	minute/minutes
m.p.	melting point
MS	Mass Spectrometry
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	trifluoromethanesulfonate
PG	Polyethylene Glycol
Ph	Phenyl
PMA	Phosphomolybdic acid
pp	polypropylene
ppm	parts per million
Pr	Propyl
PS	Polystyrene

PyBOP	Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
R	Generic alkyl group
rt	room temperature
RRTR	Resin-to-Resin Transfer Reaction
s	singlet
SPOS	Solid Phase Organic Synthesis
t	triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
UV	Ultraviolet

Chapter 1

Introduction : Applications of Boronic Acids and their Esters in Organic Chemistry

1.1 Introduction

Over the last two decades, boronic acids have become an extremely important class of organic compounds. They are employed in a variety of biological and medicinal applications such as carbohydrate recognition,[1,2] protease enzyme inhibition,[2,3] neutron capture therapy for cancer,[2,4] and trans-membrane transport.[5] In recent years, they have also gained tremendous popularity as substrates and building blocks in organic synthesis and combinatorial chemistry. The well-established Suzuki-Miyaura cross-coupling[6] has recently been complemented by a wide variety of novel, synthetically useful methodologies that employ boronic acids as substrates. Among these reactions are included the rhodium(I)-catalyzed addition to aldehydes,[7] the copper diacetate-promoted cross-coupling with nitrogen and oxygen functionalities,[8] and the three-component borono-Mannich reaction.[9]

Despite their usefulness, there are still relatively few boronic acids on the market, in comparison to amines, carboxylic acids and other more common classes of reagents. Their paucity can be explained by the difficulties associated with the synthesis and derivatization of even the simplest functionalized ones by solution phase methods. The isolation of compounds containing a boronic acid functionality can prove to be notoriously troublesome as a result of their amphiphilic character. Boronic acids are also typically slow-moving on silica gel and, consequently, must often be purified by recrystallization, a generally difficult process for this type of compounds.

1.2 Boronic acids and boronic esters

1.2.1 Stability of boronic acids

Boronic acids usually exist as crystalline solids. Aryl- and alkenylboronic acids tend to be relatively stable towards oxidation, but alkylboronic acids often decompose rapidly upon exposure to air (Figure 1-1).

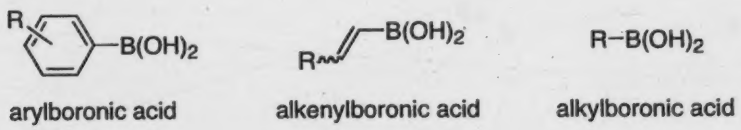


Figure 1-1. Types of boronic acids

Boronic acids are usually stable enough to be handled in ambient air, but they tend to form anhydrides, or boroxins, upon drying under vacuum. These anhydrides often decompose rapidly[10] and this observation has popularized the use of boronic esters as boronic acid surrogates (*vide infra*). As there usually is a small amount of anhydrides present in boronic acids, it is also difficult to obtain pure samples for analysis.

1.2.2 Conversion of boronic acids to boronic esters

Boronic acids react with alcohols to yield boronic esters and two equivalents of water (Equation 1-1). The reaction being reversible, the water must be removed in order to drive the reaction to completion. Typically, the water is trapped using a Dean-Stark apparatus or it is azeotropically distilled with excess alcohol.

Equation 1-1

Using a diol instead of a simple alcohol results in a shift of the thermodynamic equilibrium of the reaction favouring the products. This observation can be explained by an entropy difference, as the reaction generates three moles of products for only two moles of reactants (Equation 1-2).

Equation 1-2

Most boronic esters derived from unhindered diols can be cleaved back to the corresponding boronic acid through simple hydrolysis. However, sterically hindered diols such as pinacol and pinanediol (Figure 1-2) form boronic esters that are very robust towards hydrolysis.[11] Although this feature has made them very popular in organoboronate chemistry, these diols can not be considered protective groups since the recovery of the boronic acid functionality is, at best, very difficult.

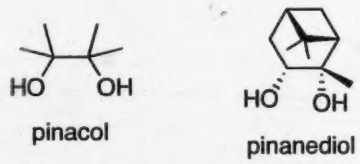
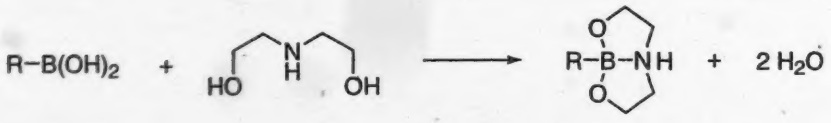


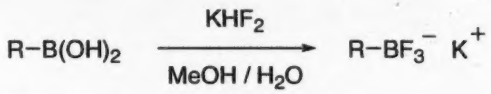
Figure 1-2. Structures of pinacol and pinanediol

A special type of diol that has also attracted attention is diethanolamine and its derivatives.[12] It generally forms stable crystalline adducts with boronic acids, which can easily be hydrolysed by simply mixing them with water (Equation 1-3).



Equation 1-3

Recently, a convenient method for the conversion of boronic acids to their potassium trifluoroborate equivalent was described (Equation 1-4).[13] This type of boronic acid derivative shows remarkable stability and can be easily purified by recrystallization.

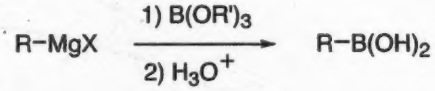


Equation 1-4

1.3 Synthesis of boronates

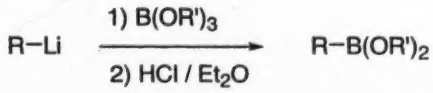
1.3.1 Reactions of organometallics with borates

Among the many ways available to synthesize boronic acids, the reaction of an organometallic species with a borate remains the most commonly used. Typically, a Grignard reagent or an organolithium is reacted at low temperature with a trialkylborate, and the resulting borate anion is quenched with aqueous acid to generate the desired boronic acid (Equation 1-5).[10]



Equation 1-5

Alternatively, the intermediate borate anion can be treated with anhydrous acid to generate the corresponding boronic ester (Equation 1-6).[14]

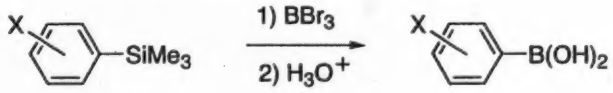


Equation 1-6

Although this method has proven quite reliable for the preparation of relatively simple boronic acids, the high basicity and nucleophilicity associated with the organometallic species make it incompatible with many functional groups.

1.3.2 Reactions of organosilanes with trihaloboranes

Recently,[15] a new preparation was reported in which an organosilane is reacted with a trihaloborane to yield a boronic acid following acid hydrolysis (Equation 1-7).

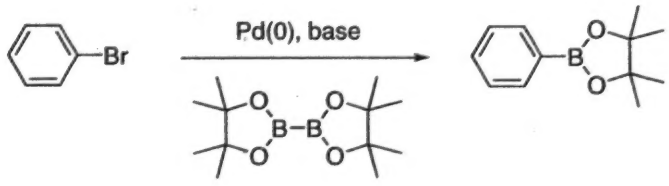


Equation 1-7

Although the reaction conditions are somewhat milder than that of the preceding route, the organosilane itself is usually prepared from a Grignard reagent or an organolithium. Additionally, this method is not suitable for compounds containing acid-sensitive functionalities.

1.3.3 Coupling of halides with diboron species

The coupling of aryl and alkenyl halides or triflates with various diboron species under Pd(0) catalysis has emerged as one of the most popular routes to boronic esters (Equation 1-8).[16] One of its main advantages is the high tolerance for a wide variety of functional groups. On the other hand, it has not yet proven useful for the synthesis of free boronic acids.



Equation 1-8

1.3.4 Hydroboration

Another common route to boronates goes through the hydroboration of alkenes and alkynes.[17] The first reaction of this type was reported by Brown and Subba Rao in 1956,[18] when they used diborane (B_2H_6) as the hydroborating agent. Since that first report, numerous reagents have been developed to perform hydroborations. Among the most commonly used ones are disiamylborane, thexylborane, 9-BBN, dicyclohexylborane, di(isopropylpropenyl)borane, catecholborane, and dibromoborane (Figure 1-3).

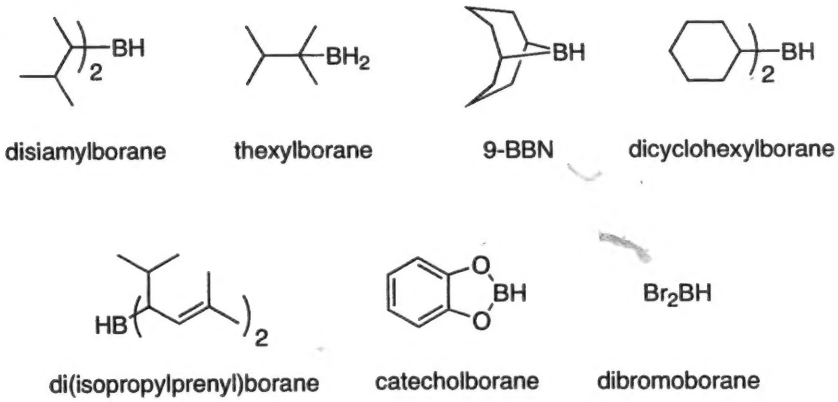
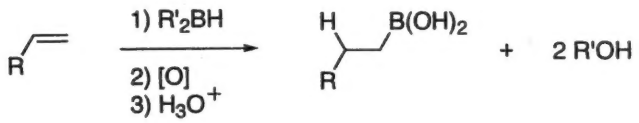
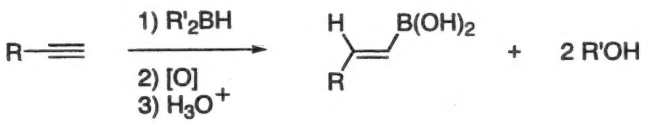


Figure 1-3. Common hydroboration reagents

When one of these reagents is reacted with an alkene, an alkylboronic acid is obtained following oxidation and/or hydrolysis (Equation 1-9). On the other hand, when an alkyne is subjected to similar reaction conditions, an alkenylboronic acid is usually obtained (Equation 1-10).



Equation 1-9

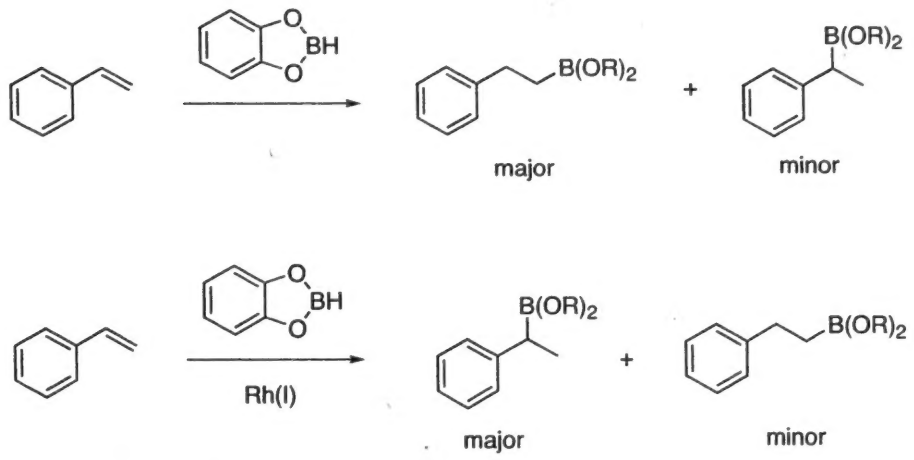


Equation 1-10

Although hydroboration followed by hydrolysis can give access to boronic acids, purification of the product can prove very troublesome. All the reagents cited above (except for dibromoborane) give rise to an alcohol or diol side-product of high boiling point, which tends to condense with the boronic acid during concentration, giving a boronic ester. For all these reasons, products of hydroboration tend to be isolated as the boronic ester instead of the acid. Dibromoborane does not suffer from this drawback because there is no alcohol produced at the end of the reaction. However, it is a very powerful reagent and, as such, it tends to react with a variety of other functional groups to yield undesired products.

1.3.5 Rhodium-catalyzed hydroboration

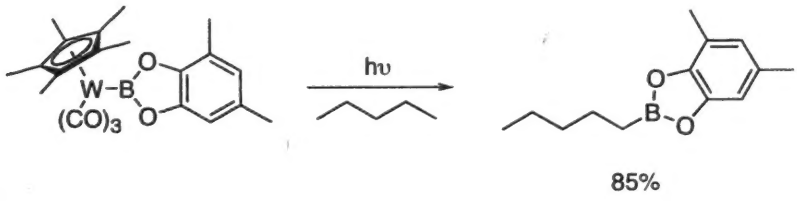
In 1985, Mannig and Noth reported the first example of hydroboration of an olefin catalyzed by rhodium.[19] The rhodium-catalyzed method is complementary to the non-catalyzed method because many substrates undergo a reversal of regioselectivity under the catalyzed conditions (Scheme 1-1). As is the case for the non-catalyzed hydroboration, the catalytic method is most useful for accessing boronic esters instead of the free boronic acids.



Scheme 1-1

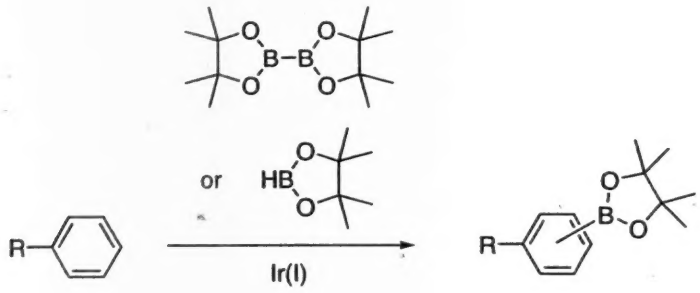
1.3.6 Transition metal-mediated borylation

In a recent study on regioselective C-H bond activation, Hartwig and co-workers reported the use of boron-containing transition metal complexes for the formation of simple organoboronates.[20] A thorough investigation revealed that a variety of alkanes can be functionalized at the terminal position to incorporate a catecholboronate or a pinacolboronate moiety (Equation 1-11).



Equation 1-11

Shortly afterwards, various complexes of iridium were shown to catalyze the borylation of arenes through C-H bond activation under mild conditions (Equation 1-12).[21] As the reaction was observed to be under steric control, mixtures of *meta* and *para* products were usually obtained. This new methodology has so far only been applied to the synthesis of pinacol esters.



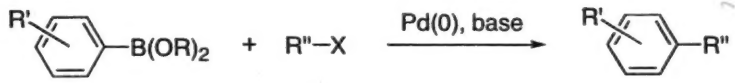
Equation 1-12

1.4 Selected examples of synthetic applications of boronates

As was briefly discussed at the beginning of this chapter, a wide variety of reactions can be performed using boronic acids and esters. This section is not intended to be an exhaustive description of all available reactions, but an overview of the work related to the applications described in Chapters 4-6.

1.4.1 Suzuki reaction

Over the past twenty years, the Suzuki reaction, also known as the Suzuki-Miyaura reaction, has become a widely used synthetic tool.[6] It involves the coupling of an organoboronate with an aryl- or an alkenylhalide in the presence of a base under palladium(0) catalysis (Equation 1-13). Its usefulness is underlined by the wide variety of functional groups that are tolerated in the process.



R" = aryl, alkenyl

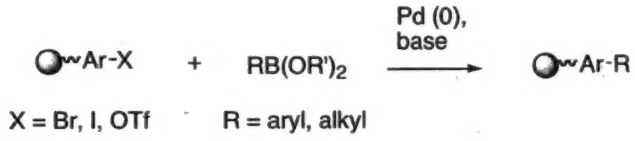
Equation 1-13

A tremendous number of studies have been aimed at improving the scope of the reaction through use of various bases, ligands, palladium sources and solvents,[6] and this area of study is still very active.

At the same time that the Suzuki reaction was becoming increasingly popular, the use of solid supports in organic synthesis was increasing at a quick pace. After having been developed as a tool for peptide synthesis by Merrifield,[22] polymeric supports have been used for a wide variety of synthetic applications. In particular, the application of the Suzuki reaction to solid phase chemistry has attracted a lot of attention over the past 10 years.[23] In fact, this reaction has been shown to constitute a very reliable way to access

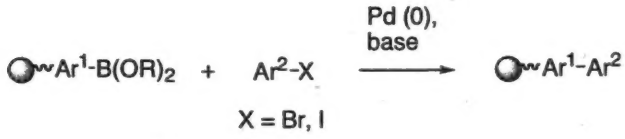
complex structures through a productive carbon-carbon bond formation. The high tolerance for functional groups of the Suzuki coupling, along with its synthetic usefulness makes it an ideal tool for combinatorial chemistry, in which a great variety of structures and functionalities need to be constructed in a highly reliable fashion.

As is presented in Chapter 4, most strategies employed so far have relied on the attachment of the halide coupling partner onto a solid support (Equation 1-14), with the boronic acid or ester counterpart present in the solution phase.



Equation 1-14

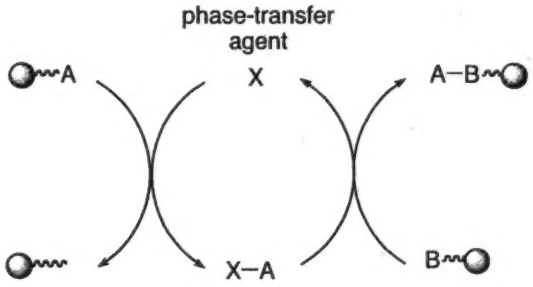
The reverse approach, in which the boronate coupling partner is polymer-bound and the halide is in solution, has also been reported (Equation 1-15).[23]



Equation 1-15

Due to the limited availability of functionalized boronic acids, most examples of Suzuki cross-coupling on solid support have resulted in relatively simple products bearing few functional groups. A simple strategy that could help circumvent this problem is the use of a versatile solid support for the derivatization of boronic acids coupled with a resin-to-resin transfer Suzuki reaction.

Resin-to-resin transfer reactions (RRTR) constitute a type of multi-resin system that further simplifies the practice of solid phase organic synthesis (SPOS). In RRTR systems, a resin-bound substrate is transferred to the solution phase by the action of a phase-transfer agent and then coupled *in situ* to another resin-bound substrate (Scheme 1-2).



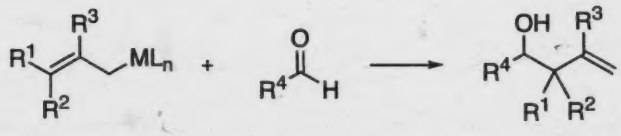
Scheme 1-2

We envisioned the derivatization of a simple boronic acid precursor into a more highly functionalized boronic acid on solid support, followed by a RRTR Suzuki coupling to a solid-supported aryl halide. This concept allows for the convergent solid-phase synthesis and eventual coupling of fragments for which a linear SPOS strategy

would involve incompatible reaction conditions. The development of the first solid support for the immobilization and derivatization of boronic acids is presented in Chapter 2. Following this initial work, we applied the concept of RRTR for the coupling of functionalized boronic acids with solid-supported aryl halides. This work, as well as more information on RRTR systems, is described in detail in Chapter 4.

1.4.2 Enantioselective allylboration of aldehydes

The enantioselective allylation, methallylation, and crotylation of aldehydes is a very important area of research for organic synthesis.[24] Despite intensive research by various groups in this field, there is no general method using simple and stable allylation reagents for the stereocontrolled formation of a wide variety of homoallylic alcohols (Equation 1-16).



Equation 1-16

Whereas many highly enantioselective allylation methods (Equation 1-16, R^1, R^2, R^3 = H) have been developed,[25] few of these procedures have been successfully extended to the enantioselective methallylation (Equation 1-16, R^1, R^2 = H, R^3 = Me) and crotylation (Equation 1-16, R^3 = H, R^1, R^2 = H, Me or Me, H) of aldehydes.

In fact, the particular problem of diastereo- and enantioselective crotylation of aldehydes remains challenging. Despite numerous reports on the subject, a method that provides both *syn* and *anti* products in a predictable fashion and in a highly enantioselective manner (>95% ee) is still elusive. Because of the high diastereoselectivity associated with allylboron reagents, many research groups have focused on the development of chiral crotylboranes and boronates.[26] Although these reagents generally give excellent diastereoselectivity in the crotylation of aldehydes, the ones that also provide high enantioselectivity are either unstable or difficult to prepare.

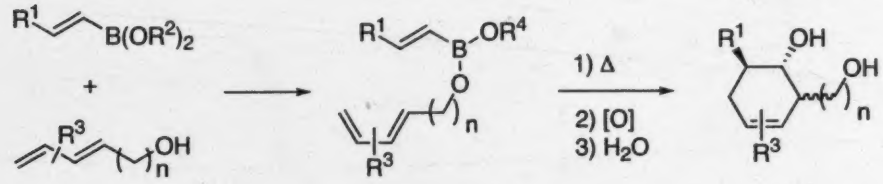
During the course of investigations on the addition of allylboronates to aldehydes in our group, Kennedy and Hall discovered that this reaction can be catalyzed by Lewis acids.[27] In view of these findings, we decided to revisit some easily accessible allylboronates in order to probe their reactivity and selectivity under the newly discovered catalytic conditions. Our results in this area are presented in Chapter 5.

1.4.3 Stereoselective cycloaddition reactions of alkenylboronates

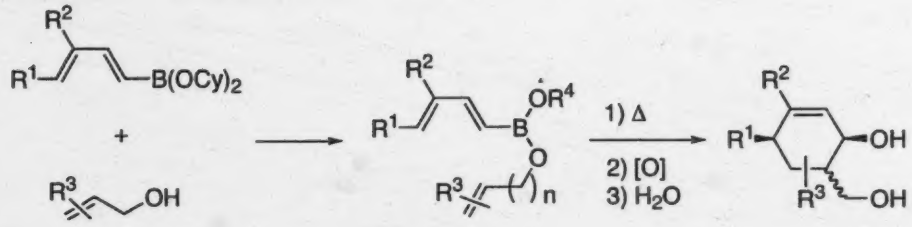
Cycloaddition reactions are of tremendous importance in organic chemistry. This fact can be explained by the simultaneous construction of several bonds, usually in a stereoselective fashion. The use of boronates as reaction partners in this type of reaction has several advantages. First, alkenyl- and dienylboronates can be accessed relatively easily through hydroboration. Second, the alkenylboronate functionality can be regarded

as an enol equivalent. Third, the alcohol subtituents on the boronate can easily be exchanged to tune the reactivity and selectivity of the reaction.

This last aspect was efficiently exploited by Batey and co-workers during their studies on the Diels-Alder reaction involving alkenylboronates and unsaturated alcohols. In one report, various alkenylboronic acids were reacted with hydroxydienes to provide the corresponding cycloadducts (Scheme 1-3).[28] In another report, dienylboronic esters were reacted with allylic alcohols to give access to the cycloadduct (Scheme 1-4).[29] In both cases, it was determined that the Diels-Alder reaction proceeds intramolecularly, underlining the importance of the easy exchange of ligands in the boronate.



Scheme 1-3



Scheme 1-4

Another study on cycloadditions with alkenylboronates involved the formation of their diethanolamine complexes.[30] The formation of a diethanolamine adduct was intended to increase the electron density of the dienylboronate and thus its reactivity with dienophiles (Figure 1-4).

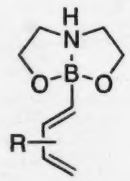


Figure 1-4. Dienylboronic acid-diethanolamine complex

In subsequent reports, the groups of Vaultier[31] and Marsden[32] also reported the use of alkenylboronic acid-diethanolamine adducts in cycloadditions. By use of chiral diethanolamine derivatives, modest levels of enantioselectivity were achieved.

1.5 Thesis objectives

This thesis addresses a number of problems related to the preparation and synthetic applications of boronic acid derivatives. In particular, the evident need for a solid support that would selectively and efficiently immobilize boronic acids represents our initial impetus. Given the stable nature of boronic acid-diethanolamine adducts as well as their ease of hydrolysis, a diethanolamine-based linker is developed as the first

solid support for the immobilization and derivatization of boronic acids. This work is presented in Chapter 2.

Next, we address the problem of alkenylboronic acid synthesis. As seen earlier, there still lacks a general way to access free alkenylboronic acids that tolerates a wide range of functional groups. We believe that the hydroboration of alkynes using diisopinocampheylborane along with an appropriate workup procedure will solve the problems associated with the synthesis of alkenylboronic acids. Our work in this area is presented in Chapter 3.

In the second part of this thesis, various applications of boronic acids and their derivatives will be reported. We first set out to demonstrate the usefulness of our recently developed resin in resin-to-resin applications. Specifically, the development of conditions for the coupling of solid-supported functionalized boronic acids with solid-supported haloarenes is investigated. As will be described in detail in Chapter 4, several advantages arise from the use of two different solid supports in a single reaction vessel. These advantages are clearly demonstrated by our results for Suzuki couplings and in the synthesis of a small model library of biphenyl derivatives.

Chapter 5 concerns the application of Lewis acid catalysis in the asymmetric addition of allylboronates to aldehydes. Despite intensive research in that area, all available methods face serious shortcomings. We decided to investigate the use Lewis acid catalysts in the allylboration, methallylboration, and crotylboration of aldehydes.

Finally, we set out to develop an organocatalytic system based on chiral diethanolamine derivatives. The objective is to take advantage of both the activation of boronic acids by diethanolamine and the easy exchange of ligands on boronic acids. With this in mind, both the Diels-Alder and the [3+2] cycloaddition reactions will be studied using various chiral diethanolamine derivatives. Our results in this area are presented in Chapter 6.

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Chapter 2

Use of DEAM-PS for the Synthesis of Arylboronic Acids

2.1 Introduction

Despite their usefulness as a class of organic compounds, boronic acids have acquired a certain notoriety in the chemical community as being difficult to handle and to purify. Even the simplest functionalized derivatives can prove to be very troublesome. Part of the difficulties arise from the amphiphilic character of certain boronic acids. Additionally, whereas arylboronic acids are usually stable on silica, they tend to elute slowly and to streak due to the constant formation and dissociation of anhydrides. On the other hand, alkenyl- and alkylboronic acids typically undergo rapid decomposition when subjected to silica gel chromatography. Boronic acids are thus traditionally purified by recrystallization. This solution is not generally applicable however, as boronic acids tend to be amorphous rather than crystalline solids. For these reasons, the boronic acid functionality is usually incorporated at a late stage in the synthesis of organoboronates for use as synthetic intermediates. Unfortunately, there are only a limited number of synthetic methods available to access boronic acids, and these methods show limited compatibility with certain functional groups. Therefore, it would be highly desirable to introduce the boronic acid functionality early in a synthesis, as long as a reliable method exists with which to purify the products. We thus set out to find both general and reliable

ways to access and purify boronic acids. This chapter describes the development and applications of DEAM-PS (**1**), the first solid support for the immobilization and purification of boronic acids (Figure 2-1).

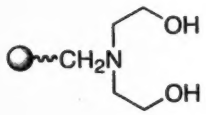

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Figure 2-1. DEAM-PS

Peptides constitute another class of organic compounds which have long been associated with difficulties in both synthesis and purification. Following groundbreaking work by Merrifield,[1] the immobilization of these substrates onto a solid support has practically solved the above-mentioned problems. Inspired by this precedent, we decided to study the possibility of immobilizing boronic acids onto a solid support in order to alleviate their well-known drawbacks.

When work on this project was initiated, there were no reports of a solid support specific for boronic acids. However, since our first article in this area was published,[2] several contributions from different groups have appeared in the literature.

One of these other supports was based on a 1,3-propanediol derivative (**2**) (Figure 2-2).[3] Although this linker proved to be robust to various reaction conditions, it also proved to be quite resistant to hydrolysis of the appended boronic acid. As a

consequence, harsh cleavage conditions were required (i.e., reflux in a MeOH/THF/CH_2Cl_2 mixture and Soxhlet extraction for two days).

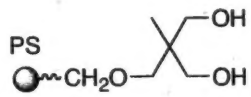

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Figure 2-2. Propanediol-based linker

Two other linkers reported at approximately the same time relied on a pinacol-like framework (**3**, **4**) (Figure 2-3).[4,5] These linkers suffer from a lengthy multi-step synthesis before attachment onto a solid support. No systematic study was conducted to determine the binding properties of these linkers to boronic acids or the possibility for further derivatization of the supported boronic acids.

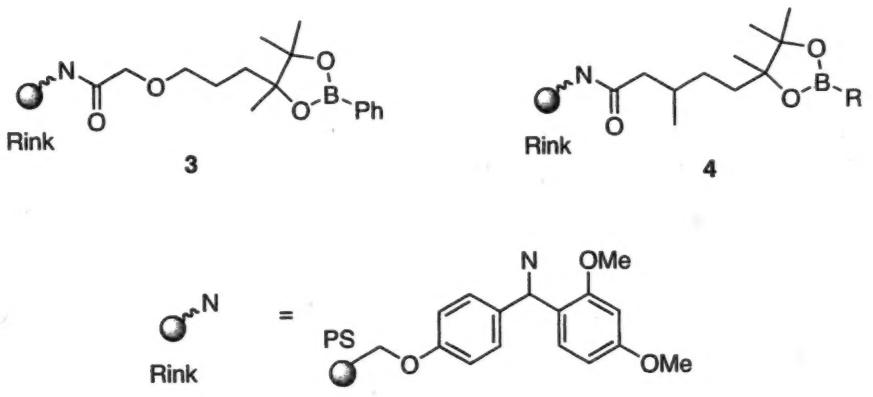

Figure 2-3. Pinacol-based linkers

A catechol-substituted polystyrene resin (**5**) has also been used for boronic acid immobilization and derivatization (Figure 2-4).[6] Recent preliminary results show this support to be efficient in these two applications, although a four-step synthesis is required prior to functionalization of the solid support.

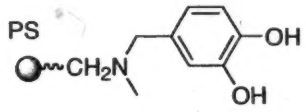

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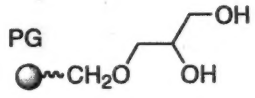
Figure 2-4. Catechol-based linker

More recently, a commercially available soluble polyglycerol matrix (**6**) was employed for the immobilization and subsequent Suzuki reaction of arylboronic acids (Figure 2-5).[7] The main advantages of this linker are its solubility in organic solvents and its very high loading (4.1 mmol g^{-1}). No study was conducted on the possible derivatization and cleavage of the supported boronic acids.



6

Figure 2-5. Polyglycerol resin

Our contribution in this field introduced the first solid support for the immobilization and derivatization of boronic acids and will be described in detail in this chapter.

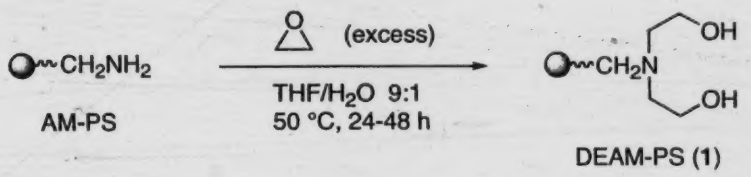
2.2 Development of a solid support for boronic acids

In view of all the above-mentioned impediments to handling boronic acids by solution phase methods, it is clear that a simple and general solid-phase approach for their immobilization and derivatization would be tremendously useful. Indeed, solid-phase methods circumvent the need for aqueous work-ups and other time-consuming operations required to isolate the desired boronic acid from excess reagents and by-products.

At the outset, there were no solid supports available to selectively immobilize boronic acids. Ideally, such a support would allow us to immobilize and cleave boronic acids under mild conditions. Additionally, it should allow us to derivatize these compounds after immobilization by performing functional group transformations at other reaction centers in the molecule.

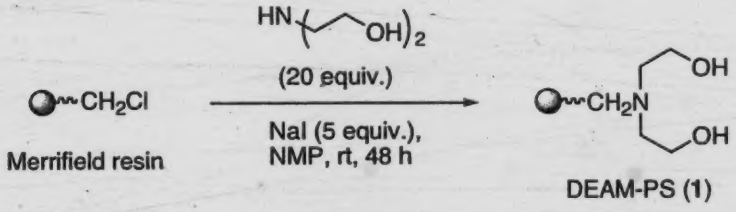
Given the ease of formation and hydrolysis of the adducts it forms with boronic acids, diethanolamine was seen as a good starting point for the design of an anchoring group for boronic acids. In our original procedure,[2] aminomethylated polystyrene (AM-PS) was reacted with ethylene oxide to yield *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS, **1**) (Scheme 2-1). The resulting resin possessed characteristics and a loading

level that suggested clean and complete dialkylation of AM-PS to DEAM-PS. Although the resin obtained from this procedure gave good results in subsequent applications, we were concerned by the use of a volatile liquid and the need for a pressure tube. Also, this protocol was not convenient for the synthesis of large amounts of resin. Therefore, we decided to investigate a new, simplified route to DEAM-PS.



Scheme 2-1

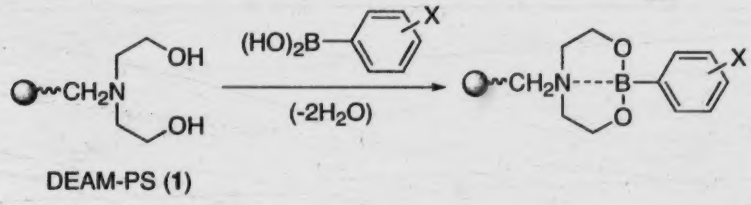
To this end, we found that DEAM-PS could be made with ease from chloromethylated polystyrene (Merrifield resin) and diethanolamine in the presence of sodium iodide in NMP at room temperature (Scheme 2-2).[8] While the latter method is more conveniently done than the original route, both methods afford DEAM-PS resin of similar characteristics with identical efficiency at immobilizing boronic acids.



Scheme 2-2

2.3 Immobilization and cleavage of boronic acids

During our initial studies on the efficiency of DEAM-PS resin, we found that *p*-tolylboronic acid can be immobilized in high yields by esterification with **1** (Scheme 2-3), through simple mixing of the acid with the resin for less than 15 minutes in anhydrous solvents at room temperature (*vide infra*).



DEAM-PS (**1**)

Scheme 2-3

As expected from the behavior of diethanolamine boronates in solution phase,[9] there was no need to drive the reaction forward through exhaustive trapping of the water released in this immobilization process. This characteristic constitutes a significant advantage over the reaction of other types of diols, whether solid-supported or not, which usually require azeotropic removal of released water.[3-7] For instance, we have confirmed the much lower efficiency of commercially available glycerol resin. Using standard immobilization conditions developed for **1**, PS-glycerol coupled to *p*-tolylboronic acid with only 50% yield.[10] These results highlight the importance of the nitrogen atom from the diol anchor of DEAM-PS. Evidence for the existence of N-B coordination in diethanolamine boronic esters has been reported with soluble adducts.[11] Such a N-B

coordination has also been observed by X-ray crystallography (see Chapter 6). Because it seems to be a crucial factor in the efficiency and ease with which DEAM-PS resin couples with boronic acids, we were interested in examining the role of the diethanolamine nitrogen in the polymer-supported case. To this end, we compared gel phase ^{1}H NMR spectra of the free form of DEAM-PS and the *p*-tolylboronic acid conjugated form (**7**) using a magic angle spinning nanoprobe (Figure 2-6).

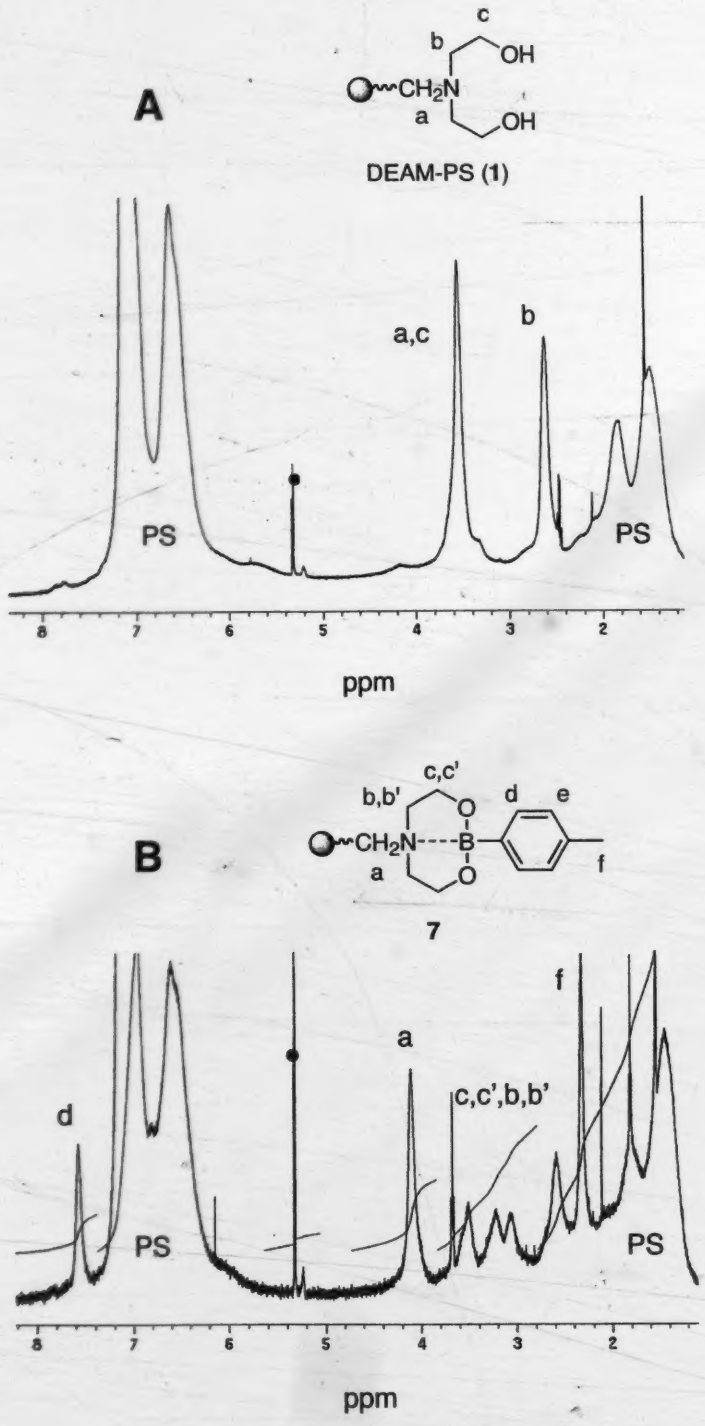
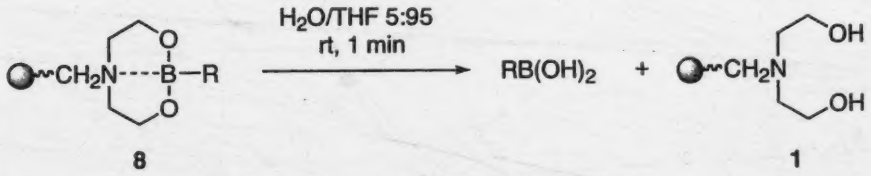


Figure 2-6. ^{1}H NMR spectra of A) DEAM-PS and B) DEAM-PS-bound *p*-tolylboronic acid (**7**) (• = CH_2Cl_2, PS = polystyrene)

In the first spectrum, two broad singlets are present at 2.6 and 3.5 ppm in the spectrum of free DEAM-PS (**A**). Presumably, the largest, most deshielded peak contains resonances from both benzylamino and hydroxymethyl methylenes. In theory, upon formation of a *cis*-fused, bicyclic diethanolamine boronate adduct whose two faces are non-equivalent, the ring hydrogens become diastereotopic. Consistent with this theory, the resulting spectrum (**B**) showed extensive degeneration of the methylenic protons in the hydroxyethyl arms, as is observed for diethanolamine-boronic acid adducts in solution (see Chapter 6). As many as four peaks were now seen between 2.2 and 3.6 ppm, thereby lending support to the formation of a tetrahedral, nitrogen-coordinated boronic ester.

We originally found a wet THF solution containing acetic acid (THF/H_2O/AcOH 90:5:5) to be effective for the release of DEAM-PS-supported boronic acids.[2] We later found that no acid is necessary and that a 95:5 THF/H_2O solution alone is sufficient to quickly liberate the boronic acids from the support (Scheme 2-4).



Scheme 2-4

To avoid product contamination and boronic acid oxidation into the corresponding phenol, it is preferable to employ a cleavage solution prepared from air- and peroxide-

free, freshly distilled THF.[a] Investigations were carried out to determine the extent to which the diethanolamine boronate linkage is sensitive to water.[12] From these studies, it was found that the extent of *p*-tolylboronic acid release rapidly reached a plateau within less than one minute. These studies also confirmed that hydrolysis is an equilibrium process, and that a large excess of water (>32 equivalents) is required to provide a practically quantitative hydrolysis. As a rule of thumb, such a quantity of water corresponds roughly to the use of 10 mL of cleavage solution (5% water/THF) per gram of resin at a 0.8 mmol g^{-1} resin loading. The above hydrolysis study also suggests that the reverse process – boronic acid immobilization onto DEAM-PS – which releases two molar equivalents of water, cannot be quantitative in THF unless an excess of boronic acid is employed to shift the equilibrium. Otherwise, according to the work of Thompson,[12] the approximate maximum yield of immobilization for equimolar amounts of DEAM-PS and boronic acid is 80%.

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[a] The 2,6-di-*t*-butyl-*p*-cresol used as stabilizer in non-distilled THF was found to accumulate in the polymer matrix of DEAM-PS and contaminate products upon cleavage. This can be prevented by the use of distilled THF for resin washing and for the cleavage solution. However, in the absence of the stabilizer, freshly distilled THF must be used in order to avoid a presumed build-up of peroxides, which have caused oxidation of the boronic acids into the corresponding phenols.

A solvent profile study using *p*-tolylboronic acid revealed that a wide range of anhydrous solvents can be employed for the immobilization (Table 2-1, entries 1-6). Whereas THF was found to be a good general solvent to solubilize and immobilize boronic acids efficiently, we have also found that dichloromethane provides higher yields of immobilization (entries 5 vs. 6). Presumably, the limited solubility of water in dichloromethane minimizes the back reaction (hydrolysis). However, the poor solubility of most boronic acids in dichloromethane limits its usefulness. On the other hand, hydroxylic solvents such as methanol and ethanol allow a dynamic transesterification process to take place, leading to non-quantitative immobilization (entry 1). For these reasons, we opted for THF as the solvent of choice. These immobilized boronic acids were recovered intact after cleavage and the leftover DEAM-PS resin can be recycled with no apparent loss of efficiency after neutralization with base (dilute triethylamine) followed by THF and CH_2Cl_2 rinses.

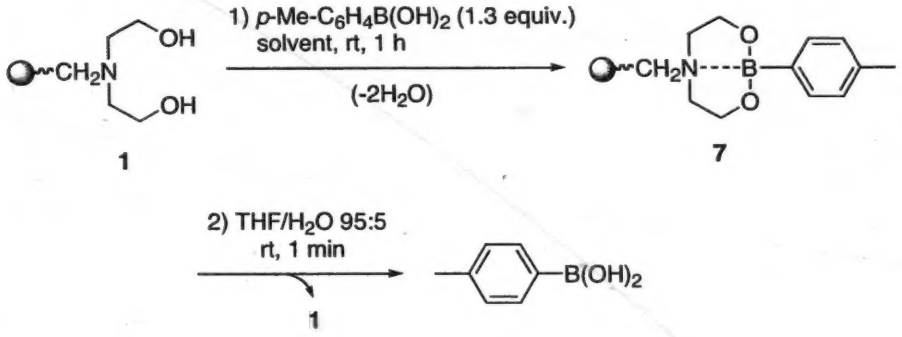


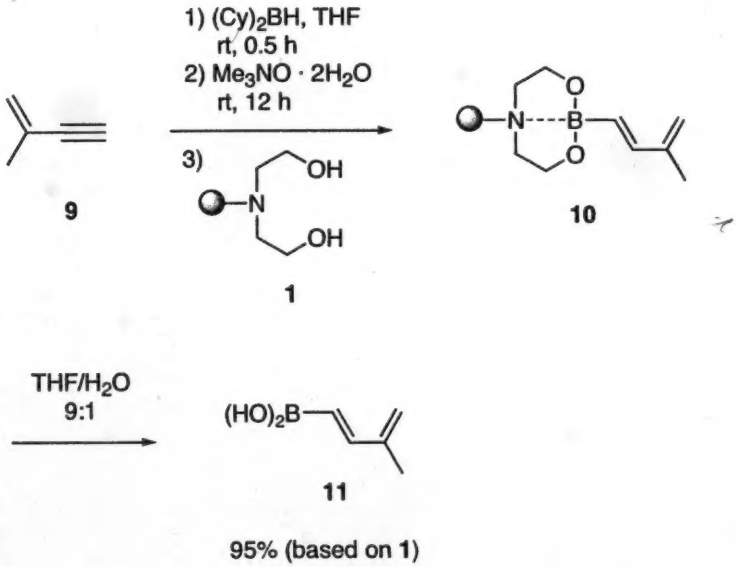
Table 2-1. Immobilization of *p*-tolylboronic acid onto DEAM-PS[a]

entry	solvent	yield (%)[b]	purity (%)[c]
1	MeOH	72	>95
2	NMP	80	>95
3	Et_2O	90	>95
4	toluene	88	>95
5	CH_2Cl_2	98	>95
6	THF	89	>95

[a] Coupling reactions were conducted by shaking resin **1** (1 equiv., 120 mg, 1.15 mmol/g) with the *p*-tolylboronic acid (1.3 equiv.) in the indicated solvent (1.5 mL) at room temperarure for 1 hour in a polypropylene fritted vessel. [b] Yields of boronic acid recovered after cleavage from the resin with 5% H_2O/THF for 1 min at rt and washed with 5% H_2O/THF (3×). The resin was rinsed with the reaction solvent (3×) prior to cleavage. For entries 4 and 5, additional THF rinses were carried out (3×). The reported yields are an average of mass balance and internal standardization (see section 2.3 for details) based on the loading of resin **1** measured by elemental analysis. [c] Estimated by comparison of ^{1}H NMR spectra of starting and recovered boronic acids.

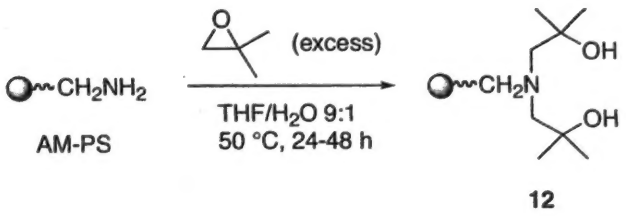
The use of scavenger resins to eliminate excess reagents is a promising strategy in the solution-phase synthesis of parallel libraries.[13] In this regard, DEAM-PS resin could be employed to scavenge unreacted boronic acids from Suzuki cross-couplings[14] and other reaction processes. Similarly, it could be utilized to capture boronic acid products from complex reaction mixtures either for purification or to perform solid-phase transformations. As a significant demonstration of such applications of DEAM-PS, it

was employed in the purification of crude dienylboronic acid **11** (Scheme 2-5).[15] The latter is produced by treating 2-methyl-1-buten-3-yne (**9**) with dicyclohexylborane followed by oxidative workup. The purification of alkenylboronic acids such as compound **11** can be quite troublesome. However, the use of DEAM-PS to capture **11** and eliminate excess reagents and the cyclohexanol oxidation by-product greatly facilitates its purification through simple rinsing of its resin-bound form **10**.



Scheme 2-5

A diisobutanolaminomethyl substituted resin (**12**) was synthesized from isobutylene oxide (Scheme 2-6) to investigate whether increased steric bulk would improve tolerance of the support to water and hydroxylic solvents. Immobilization and cleavage of *p*-tolylboronic acid from resin **12**, however, did not show any improvement in this respect when done under similar conditions as for resin **1**.



12

Scheme 2-6

The relative sensitivity of the diethanolamine boronic ester linkage to water and alcohols should be taken into account when using DEAM-PS for the derivatization of functionalized boronic acids. It appears that anhydrous and alcohol-free reaction conditions are most preferable to avoid premature cleavage of products from the resin. On the other hand, these cleavage characteristics can be significant practical aspects to derivatizing functionalized boronic acids on DEAM-PS, as they could be directly released in an aqueous buffer required for biological screening.

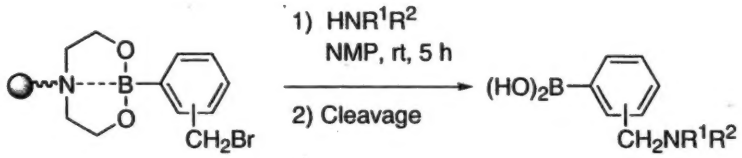
2.4 Solid phase derivatization of functionalized boronic acids

The initial aim of this project was to develop a series of useful solid-phase reaction protocols to derivatize functionalized, DEAM-PS-supported boronic acids. To evaluate the scope of reaction conditions compatible with DEAM-PS supported boronic acids, simple functional group interconversion methods were examined. All of the supported substrates were easily prepared in high yield from DEAM-PS as described in the previous section. Most boronic acid products obtained after cleavage with 5%

water/THF and concentration *in vacuo* were not further purified and were characterized by mass spectrometry, IR, and ^{1}H and ^{13}C NMR spectroscopy. In general, all compounds were obtained with a minimum of 90% purity, and in the majority of cases there were no detectable by-products by NMR analysis.

Table 2-2 summarizes the results for the nucleophilic substitution of bromomethyl-derivatized benzeneboronic acids with representative primary and secondary amines. In the synthesis of amphoteric aminomethyl-substituted products, the advantages of a solid-phase approach towards product isolation are optimal vis-à-vis solution-phase methods. Following initial studies on my part, optimization of the reaction conditions for substitutions and reductive aminations was done by Mark Zak, an undergraduate student working under my supervision. The optimal conditions found for the alkylation of *meta*- and *para*-substituted substrates **14** and **15** involve simple stirring of DEAM-PS supported bromomethylbenzeneboronic acid with the amine in NMP for approximately 5 hours at room temperature. As much as 10 equivalents of the secondary amines were employed to ensure complete reaction under these conditions. In order to suppress cross-linking by double alkylation with primary amines, it was found preferable to use a low loading DEAM-PS resin (< 0.60 mmol g^{-1}) with a larger excess of the amine (50 equiv.). Due to the large excess of primary amine reactant, the yields of the secondary amine products (compared to the tertiary amine products) may suffer more from premature cleavage of the supported boronic acid. Nonetheless, these protocols provided good to excellent yields of isolated secondary and tertiary amine products **17** and **18**. Unfortunately, these and several other conditions failed to provide any desired

alkylation product in the case of the *ortho*-substituted substrate **13**. For as yet unexplained reasons, facile premature cleavage was observed. These *ortho* aminomethyl-substituted products, however, can be obtained from reductive amination chemistry (*vide infra*).



13 *o*-, **14** *m*-, **15** *p*- **16** *o*-, **17** *m*-, **18** *p*-

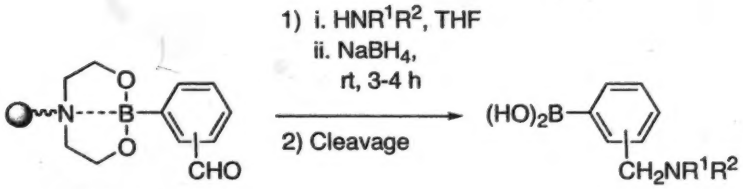
Table 2-2. Substitution reactions of bromomethyl-substituted arylboronic acids

entry	substrate	conditions[a]	product	yield[b] (%)	purity[c] (%)
1	**14**	A	**17a** {H, CH_2Ph}	69	95
2	**14**	A	**17b** {H, $CH_2CH(CH_3)_2$}	50	>90
3	**14**	B	**17c** {$(CH_2)_2O(CH_2)_2$}	85	95
4	**14**	B	**17d** {Me, CH_2Ph}	75	>95
5	**15**	A	**18a** {H, CH_2Ph}	69	>90
6	**15**	A	**18b** {H, $CH_2CH(CH_3)_2$}	53	95
7	**15**	B	**18c** {$(CH_2)_2O(CH_2)_2$}	98	>90
8	**15**	B	**18d** {Me, CH_2Ph}	94	95

[a] Reactions were performed by shaking the supported benzyl bromide with the amine in NMP at rt for approx. 5 hours (typical scale 0.12 mmol of **14** or **15**) . Conditions: A: 50 equiv. of primary amine, use of low loading DEAM-PS resin (0.60 mmol g^{-1}). B: 10 equiv. of secondary amine, use of either low loading (0.60 mmol g^{-1}) or high loading (1.14 mmol g^{-1}) DEAM-PS resin. [b] Non optimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for >12 hours. The reported values are an average of mass balance and internal standardization (see section 2.3 for details). [c] Estimated from ^1H and ^{13}C NMR data.

The results for the reductive amination of supported formyl-substituted benzeneboronic acids with various primary and secondary amines – done by Mark Zak

under my supervision – are compiled in Table 2-3. The only set of conditions found to avoid premature cleavage of the boronic acid involves pre-formation of the imine in THF, followed by addition of sodium borohydride as the hydride source. Other hydride reagents tested (e.g. $NaBH(OAc)_3$, $NaBH_3CN$) led to premature cleavage of the supported boronic acid. Interestingly, only the *ortho* substrate **19** gave satisfactory yields of products **16a-d** with a good purity. This chemistry thus complements the bromomethyl substitution method described above. The less hindered *meta* and *para* substrates **20** and **21** gave the respective amine products **17** and **18** in a significantly lower purity. Although there was no evidence for double alkylation in the case of primary amines, the desired products were accompanied by unidentified impurities. In a similar way, the inverse process - reductive alkylation of supported aniline substrates - was also unsuccessful both for aromatic and aliphatic aldehydes.



19 *o*-, **20** *m*-, **21** *p*- **16** *o*-, **17** *m*-, **18** *p*-

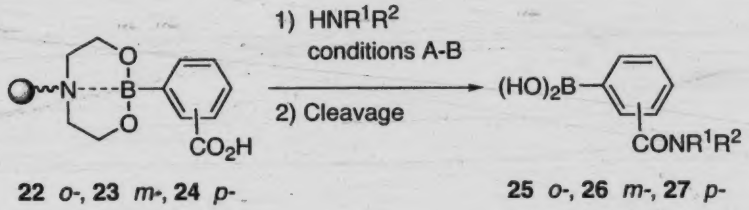
Table 2-3. Reductive amination of formyl-substituted arylboronic acids[a]

entry	substrate	product	yield[b] (%)	purity[c] (%)
1	**19**	**16a** {H, CH_2Ph}	66	>90
2	**19**	**16b** {H, $CH_2CH(CH_3)_2$}	55	>90
3	**19**	**16c** {H, $(CH_2)_3Ph$}	62	95
4	**19**	**16d** {H, $(CH_2)_3CH_3$}	73	>95

[a] Typical scale 0.1 mmol. A: Reactions were carried out by preforming the imine from supported aldehyde and the amine (2 equiv.) in THF at rt for approx. 2.5 hours. Sodium borohydride was added and the suspension was shaken for approx. 4 hours. [b] Non optimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for >12 hours. The reported values are an average of mass balance and internal standardization (see section 2.3 for details). [c]Estimated from ^1H and ^{13}C NMR data.

The formation of amide derivatives from DEAM-PS supported carboxy-functionalized arylboronic acids – performed by myself and by Christian Bérubé working under my supervision – proved very general with respect to reaction conditions (Table 2-4). A substrate limitation, however, was observed as the *ortho*-substituted substrate **22** failed to provide the expected coupling products, as it was cleaved prematurely during the reactions. The *meta*- and *para*-carboxy substituted substrates **23** and **24** provided good yields of amide products. In most cases, the use of DIC/HOBT protocols were satisfactory for the coupling of primary, secondary, and even aromatic amines (entries 4 and 11). In the most unfavorable cases, however, it was found preferable to employ coupling reagents such as PyBOP or HBTU. Moreover, we have found that the use of

these coupling reagents induces less premature cleavage as compared to the use of carbodiimide reagents.



22 *o-*, **23** *m-*, **24** *p-* **25** *o-*, **26** *m-*, **27** *p-*

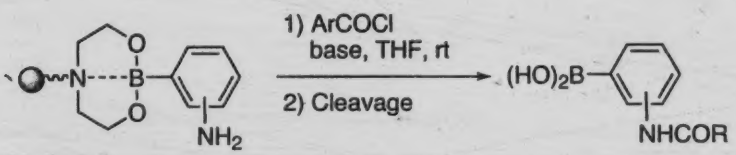
Table 2-4. Amide coupling of carboxy-substituted arylboronic acids

entry	substrate	conditions[a]	product	yield[b] (%)	purity[c] (%)
1	**23**	A	**26a** {H, $(CH_2)_3Ph$}	60	95
2	**23**	A	**26b** {H, $CH(CH_3)_2$}	60	>90
3	**23**	A	**26c** {H, $(CH_2)_3CH_3$}	56	>90
4	**23**	B	**26d** {H, Ph}	82	>95
5	**23**	A	**26e** {Et, Et}	77	90
6	**23**	A	**26f** {Bu, Bu}	79	90
7	**23**	A	**26g** {CH_2Ph, CH_2Ph}	60	>90
8	**24**	B	**27a** {H, $(CH_2)_3Ph$}	65	>95
9	**24**	B	**27b** {H, $CH(CH_3)_2$}	81	>95
10	**24**	A	**27c** {H, $(CH_2)_3CH_3$}	64	95
11	**24**	A	**27d** {H, Ph}	67	>95
12	**24**	A	**27e** {Et, Et}	59	>90
13	**24**	A	**27f** {Bu, Bu}	53	90
14	**24**	B	**27g** {CH_2Ph, CH_2Ph}	70	95
15	**24**	A	**27h** {H, $CH_2CH_2NEt_2$}	70	>95

[a] Typical scale 0.1 mmol. A: Reactions were carried out by shaking the supported carboxylic acid with the amine (4 equiv.), DIC (4 equiv.) and HOBT·H_2O (4 equiv.) in NMP or DMF at rt for 18 h. B: Reactions were carried out by shaking the supported carboxylic acid with the amine (2 equiv.), DIPEA (4 equiv.), and PyBOP (2 equiv.) in DMF at rt for 20 h. [b] Non optimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for > 12 hours. The reported values are an average of mass balance and internal standardization (see section 2.3 for details). [c] Estimated from ^1H and ^{13}C NMR data.

A notable example of amide formation with supported boronic acids involves **24** and *N,N*-diethylethylenediamine (entry 15). The resulting amphoteric *p*-borono-benzamide product **27h**, a compound with potential use in boron neutron capture therapy (BNCT),[16] was obtained pure in a 75% yield after cleavage from the resin. Previously reported syntheses of **27h** involve protection of the boronic acid and extensive manipulations such as successive recrystallizations.[16]

We have shown that anilide-derivatized boronic acids (**29**) can be obtained from the reaction of DEAM-PS-supported aminobenzeneboronic acids (**28**) with acid chlorides (Scheme 2-7).[2] Although this transformation works well in the case of aromatic acid chlorides (see Chapter 4), aliphatic acid chlorides cause premature cleavage of the supported boronic acid from the resin. It was later found that compounds of this sort can also be isolated in a variable range of yields (ca. 50-80%) by reaction of aromatic and aliphatic carboxylic acids with supported anilines **28** using standard peptide coupling chemistry.[12]



28 **29**

Scheme 2-7

In addition to these applications, other reactions – performed by other members of the Hall group – were found compatible with DEAM-PS-supported boronic acids.[12] For

example, *m*- and *p*-substituted aminobenzene-boronic acids cleanly form ureas and thioureas in high yield when reacted with isocyanates and isothiocyanates, respectively. Additionally, a Ugi four-component coupling provided a very interesting example of a multicomponent reaction using DEAM-PS resin.

All these reactions could be performed easily on gram scale, especially with the use of high loading DEAM-PS resin. The use of DEAM-PS resin for solid-phase derivatization of functionalized boronic acids is also potentially advantageous for handling and storage purposes. Indeed, boronic acids can be protected against slow air oxidation to the corresponding borates through immobilization as diethanolamine adducts.

2.5 Experimental

2.5.1 General

All starting boronic acids employed are commercially available (Lancaster, Frontier Scientific, and Combi-Blocks) and were used without purification. All other reagents are also commercially available and unless stated otherwise they were used without purification. Starting resins were purchased from Rapp-Polymere (Tübingen, Germany) and Nova-Biochem (LaJolla, CA). In most cases, the loading value stated by the supplier was used. Solid-phase reactions that required heating were performed in glassware silanized by treatment with 20% TMSCl/toluene for >12 hours. Those done at

room temperature were agitated inside polypropylene (pp) filter vessels purchased from Bio Rad (Hercules, California) and International Sorbent Technology Ltd. (Hengoed, UK). Resin washing operations were carried out on a vortexer. THF and Et_2O for reactions and cleavage (including resin washes) were dried by distillation over sodium/benzophenone ketyl and used the same day. Dichloromethane, toluene and methanol were distilled over calcium hydride. Anhydrous NMP and DMF were obtained commercially. Chemical yields of boronic acid products were compiled as an average of mass balance (assuming dehydration to the corresponding anhydrides (FW = FW – H_2O)) and internal standardization by ^1H NMR. To this end, unless indicated otherwise, ethyl acetate was used as an internal standard and it was found to provide very consistent values under a 15 sec. relaxation delay. 2,5-Dimethylfuran was employed in a few occasions.[17] Purity analysis was estimated by ^1H and ^{13}C NMR according to the following scheme: >95%: no unidentified peaks; 95%: minor amounts of barely measurable impurities; other percentages were based on the relative measure of peak heights and integrals from signals of product compared to signals from starting boronic acid and by-products. For reactions carried out in NMP, minor residual amounts of solvent sometimes present in NMR spectra were not accounted for in the evaluation of purity. ^1H NMR spectra were recorded at 300 or 500 MHz while both APT (Attached Proton Test) and BB (broad band) ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. Due to their very low intensity, ^{13}C signals arising from the quaternary carbon bearing the boronic acid group were usually missing and were therefore not listed. They were sometimes observed as broad signals in ^{13}C BB NMR spectra but were never observed in the corresponding ^{13}C APT NMR experiments. Similarly, the ^{13}C signals

arising from quaternary carbons bearing a carbonyl substituent were sometimes missing. Low resolution electrospray mass spectra were acquired using atmospheric pressure ionization (API) with a quadrupole mass analyser (positive mode). High-resolution (HRMS) analysis were obtained on a time-of-flight instrument. A 1:1 mixture of MeCN/H_2O was used as the solvent for mass spectral analysis of boronic acids. It was important not to use an alcohol as solvent for the mass spectral analysis of boronic acids in order to avoid observing their corresponding boronate esters. UV analysis was carried out using a Varian Cary 400 UV-visible spectrophotometer. IR spectra were acquired on a Nicolet Magna 750 IR Spectrometer and a Nic-Plan IR Microscope.

2.5.2 Synthesis of *N,N*-diethanolaminomethylpolystyrene (DEAM-PS) (1)

Chloromethyl polystyrene resin (3.00 g, 3.72 mmol, theoretical loading: 1.24 mmol g^{-1}, 200-400 mesh) was weighed into a 70 ml pp reaction vessel and swollen in dry NMP (32 mL). Diethanolamine (7.13 mL, 74.4 mmol) was added and the mixture was vortexed for a short time. NaI (2.79 g, 18.6 mmol) was added as a solid and the resin suspension was shaken at rt for > 48 h. The reaction mixture was drained, and the resin was rinsed with 2:1 THF/H_2O (3 ×), 1:1 DMF/Et_3N (3 ×), dry THF (3 ×), and CH_2Cl_2 (5 ×). The resin was then dried under high vacuum for > 24 h to afford a white resin (3.03 g, theoretical: 3.26 g, theoretical loading: 1.14 mmol g^{-1}); FTIR (microscope): 3430, 3060, 3026, 2923, 1601, 1493, 1452 cm^{-1}.

2.5.3 Immobilization and cleavage of boronic acids to and from DEAM-PS

Typical procedure:

p-tolylboronic acid (20 mg, 0.152 mmol) and THF (1.5 mL) were added to DEAM-PS **1** (102 mg, 0.117 mmol, experimental loading: 1.15 mmol g^{-1}) in a pp reaction vessel. The reaction suspension was shaken at room temperature for 1 hour and the pp vessel was drained. The resin was then washed with dry THF (3 × 2 mL). The resin-bound boronic acid **7** was cleaved by vortexing the resin with 5% H_2O/THF (2 mL) for 1 minute at room temperature. The product-containing solution was drained and the resin was washed with 5% H_2O/THF (3 × 2 mL). The filtrates were combined, concentrated under reduced pressure and dried under high vacuum overnight to afford *p*-tolylboronic acid as a white solid (12 mg, 87% yield by mass; 91% yield by ^{1}H NMR with EtOAc internal standard).

2.5.4 Substitution of DEAM-PS-supported bromomethyl-substituted arylboronic acids

Typical procedure:

3-(benzylaminomethyl)phenylboronic acid (17a)

The DEAM-PS resin (**1**) (200 mg, 0.120 mmol, theoretical loading: 0.60 mmol g^{-1}), and 3-bromomethylphenyl boronic acid (34 mg, 0.16 mmol) were weighed into a 10 mL pp reaction vessel. Dry CH_2Cl_2 (2 mL) was added and the reaction suspension was shaken for 1.5 hour at room temperature. The pp vessel was drained, and the resin was washed with dry CH_2Cl_2 (3 × 2 mL). The resin was then swollen in dry NMP (2 mL), and benzylamine (0.655 mL, 6.0 mmol) was added. The reaction vessel was shaken for 5

hours, then drained and the resin was washed successively with dry DMF (3 ×), dry CH_2Cl_2 (5 ×), and dry THF (5 ×). The product was then cleaved from the resin by vortexing the resin using the typical procedure described above (5% H_2O/THF for 20 minutes). The product containing solution was drained and the resin was washed with 5% H_2O/THF (3 ×). The product filtrates were combined, concentrated under reduced pressure and dried under high vacuum overnight to afford a white solid (19 mg, 70% yield by mass; 67% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.66 (m, 2H), 7.36-7.30 (m, 7H), 3.84 (s, 2H), 3.83 (s, 2H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 135.6, 135.2, 134.2, 131.0, 129.9, 129.7, 129.2, 128.8, 128.7, 53.5, 53.1; IR (CH_2Cl_2 cast) 3360, 3029, 2925, 2852, 1652, 1602 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{14}H_{17}BNO_2$ $(M+H)^+$ 242.1347, found 242.1350.

3-(*iso*-Butylaminomethyl)phenylboronic acid (17b)

White solid (52% yield by mass; 48% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.62-7.61 (m, 2H), 7.29-7.28 (m, 2H), 3.94 (s, 2H), 2.62 (d, J = 6 Hz, 2H), 1.91 (tqq, J = 7, 7, 7 Hz, 1H), 0.95 (d, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 135.7, 135.3, 134.6, 130.3, 128.6, 56.6, 54.1, 28.1, 20.7; IR (CH_2Cl_2 cast) 3259, 3046, 2956, 2871, 1665, 1602 cm^{-1}; HRMS (ES *m/z*) calcd for $C_{11}H_{19}BNO_2$ $(M+H)^+$ 208.1503, found 208.1501.

3-(Morpholinomethyl)phenylboronic acid (17c)

White solid (81% yield by mass; 90% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.69-7.64 (m, 2H), 7.39-7.36 (m,

1H), 7.32-7.27 (m, 1H), 3.70-3.65 (m, 4H), 3.53 (s, 2H), 2.49-2.45 (m, 4H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 141.1, 136.7, 136.4, 134.1, 132.8, 128.6, 67.5, 64.4, 54.5; IR (CH_2Cl_2 cast) 3405, 3047, 2957, 2857, 2808, 1652, 1602 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{17}BNO_3$ $(M+H)^+$ 222.1296, found 222.1297.

_N_-Methyl-3-(benzylaminomethyl)phenylboronic acid (17d)

White solid (73% yield by mass; 77% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.69-7.64 (m, 2H), 7.36-7.27 (m, 7H), 3.56 (s, 4H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 138.7, 137.6, 136.2, 134.1, 132.4, 130.7, 129.4, 128.6, 128.5, 62.7, 62.5, 42.1; IR (CH_2Cl_2 cast) 3405, 3028, 2942, 2835, 2785, 1601 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{15}H_{19}BNO_2$ $(M+H)^+$ 256.1503, found 256.1506.

4-(Benzylaminomethyl)phenylboronic acid (18a)

White solid (69% yield by mass; 69% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.72 (d, J = 8 Hz, 2H), 7.36-7.30 (m, 7H), 3.84 (s, 4H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 138.3, 135.2, 131.7, 130.0, 129.7, 129.0, 128.9, 58.9, 53.1; IR (CH_2Cl_2 cast) 3396, 3028, 2925, 2819, 1608 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{14}H_{17}BNO_2$ $(M+H)^+$ 242.1347, found 242.1344.

4-(*iso*-Butylaminomethyl)phenylboronic acid (18b)

White solid (52% yield by mass; 53% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.70 (d, J = 8 Hz, 2H), 7.32 (d, J =

8 Hz, 2H), 3.93 (s, 2H), 2.60 (d, J = 7 Hz, 2H), 1.90 (tqq, J = 7, 7, 7 Hz, 1H), 0.95 (d, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 135.2, 134.9, 134.7, 129.1, 56.6, 53.7, 28.0, 20.7; IR (CH_2Cl_2 cast) 3432, 2957, 2872, 2823, 1660, 1610 cm^{-1}; HRMS (ES, m/z) calcd for $C_{11}H_{19}BNO_2$ $(M+H)^+$ 208.1503, found 208.1506.

4-(Morpholinomethyl)phenylboronic acid (18c)

White solid (88% yield by mass): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.72 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 3.72-3.68 (m, 4H), 3.34 (s, 2H), 2.57-2.53 (m, 4H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 138.8, 135.1, 130.1, 67.3, 64.0, 54.3; IR (CH_2Cl_2 cast) 3406, 2957, 2859, 2811, 1657, 1609 cm^{-1}; HRMS (ES, m/z) calcd for $C_{11}H_{17}BNO_3$ $(M+H)^+$ 222.1296, found 222.1294.

4-(Benzylaminomethyl)phenylboronic acid (18d)

White solid (89% yield by mass; 99% yield by ^{1}H NMR with 2,5-dimethylfuran internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.73 (d, J = 8 Hz, 2H), 7.35-7.31 (m, 7H), 3.64 (s, 4H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, 5% D_2O in CD_3OD) δ 137.9, 135.1, 134.8, 130.8, 129.9, 129.5, 128.9, 62.3, 62.3, 41.9; IR (CH_2Cl_2 cast) 3408, 3027, 2927, 2838, 2787, 1609 cm^{-1}; HRMS (ES, m/z) calcd for $C_{15}H_{19}BNO_2$ $(M+H)^+$ 256.1503, found 256.1504.

2.5.5 Reductive amination of DEAM-PS-supported formyl-substituted arylboronic acids

Typical procedure:

2-(benzylaminomethyl)phenylboronic acid (16a)

DEAM-PS resin **1** (100 mg, 0.114 mmol, theoretical loading: 1.14 mmol g^{-1}) and 2-formylphenylboronic acid (23 mg, 0.15 mmol), were weighed into a pp reaction vessel. Dry CH_2Cl_2 (2 mL) was added, and the reaction suspension was shaken for 1.5 hour. The pp vessel was then drained, and the resin washed with dry CH_2Cl_2 (3 ×). The resin was swollen in dry THF (2 mL), and benzylamine (25 μL, 0.23 mmol) was added. The reaction vessel was shaken for 2.5 hours, then $NaBH_4$ (18 mg, 0.46 mmol) was added, and the vessel was shaken for an additional 3.5 hours. The pp vessel was drained, and the resin was washed successively with dry DMF (3 ×), dry CH_2Cl_2 (5 ×), and dry THF (5 ×). The product was then cleaved from the resin using the typical procedure described above (5% H_2O/THF). The product-containing solution was drained and the resin was washed with 5% H_2O/THF (3 × 2 mL). The product filtrates were combined, concentrated under reduced pressure and dried under high vacuum overnight to afford a white solid (71% yield by mass; 60% yield by ^1H NMR with 2,5-dimethylfuran internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.47-7.31 (m, 6H), 7.21-7.14 (m, 2H), 7.08-7.05 (m, 1H), 3.98 (s, 2H), 3.85 (s, 2H); ^{13}C NMR (125 MHz, 5% D_2O in CD_3OD) δ 142.4, 136.2, 131.6, 130.8, 129.9, 129.6, 129.5, 128.3, 127.7, 124.2, 54.1, 51.1; IR (CH_2Cl_2 cast) 3300, 3060, 3028, 3004, 2923, 2870, 1454 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{14}H_{17}BNO_2$ $(M+H)^+$ 242.1347, found 242.1344.

2-(*iso*-Butylaminomethyl)phenylboronic acid (16b)

White solid (57% yield by mass); ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.47-7.44 (m, 1H), 7.21-7.12 (m, 3H), 4.02 (s, 2H), 2.70 (d, J = 7 Hz, 2H), 2.10 (tq, J = 7, 6 Hz, 1H), 1.02 (d, J = 7 Hz, 6H); ^{13}C NMR (125 MHz, 5% D_2O in CD_3OD) δ 132.0, 128.2, 127.7, 124.0, 56.5, 55.4, 26.9, 20.9; IR (CH_2Cl_2 cast) 3301, 3090, 2956, 2926, 2869, 1443 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{19}BNO_2$ $(M+H)^+$ 208.1503, found 208.1503.

2-((3'-Phenyl-propylamino)methyl)phenylboronic acid (16c)

White solid (62% yield by mass; 62% yield by ^{1}H NMR with 2,5-dimethylfuran internal standard): ^{1}H NMR (300 MHz 5% D_2O in CD_3OD) δ 7.43-7.41 (m, 1H), 7.30-7.13 (m, 8H), 3.98 (s, 2H), 2.91-2.85 (m, 2H), 2.70 (t, J = 8 Hz, 2H), 2.05 (quintet, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD): δ 142.5, 131.5, 129.5, 129.4, 128.3, 127.7, 127.1, 124.0, 54.9, 34.4, 29.7; IR (CH_2Cl_2 cast) 3230, 3058, 3026, 2917, 2849, 1495 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{16}H_{21}BNO_2$ $(M+H)^+$ 270.1660, found 270.1656.

2-(*n*-Butylaminomethyl)phenylboronic acid (16d)

White solid (75% yield by mass; 71% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.45-7.42 (m, 1H), 7.20-7.14 (m, 3H), 4.00 (s, 2H), 2.86 (t, J = 8 Hz, 2H), 1.71 (quintet, J = 8 Hz, 2H), 1.41 (sextet, J = 8 Hz, 2H), 0.99 (t, J = 8 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 142.5, 131.5, 128.2, 127.7, 124.1, 54.9, 30.1, 21.4, 14.1; IR (CH_2Cl_2 cast) 3310, 3233, 3057, 3005,

2958, 2930, 2872, 1598 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{19}BNO_2$ $(M+H)^+$ 208.1503, found 208.1508.

2.5.6 Amide formation

Typical procedure for the formation of amides using DIC/HOBT (Method A): 3-(3'-Phenylpropyl-1'-amino)carbonylphenylboronic acid (26a)

In a 10 mL pp vessel, resin **23** (100 mg, 0.10 mmol) was swollen in NMP (3.5 mL). 3-Phenylpropylamine (57 μL, 0.40 mmol), HOBt·H_2O (61 mg, 0.40 mmol), and 1,3-diisopropylcarbodiimide (63 μL, 0.40 mmol) were successively added and the vessel was shaken for 20 hours at room temperature. The suspension was drained, and the resin was rinsed with NMP (3 ×), THF (5 ×), and CH_2Cl_2 (5 ×). Cleavage of the resin-bound boronic acid using the standard conditions described above, followed by concentration of the filtrates afforded **26a** as a white solid (17 mg, 60%).

Typical procedure for the formation of amides using DIPEA/PyBOP (Method B): 3-Phenylaminocarbonylphenylboronic acid (26d)

In a 10 mL pp vessel, resin **23** (80 mg, 0.08 mmol) was swollen in DMF (2 mL). Diisopropylethylamine (55 μL, 0.32 mmol), and PyBOP (84 mg, 0.16 mmol) were added and the vessel was shaken for 20 hours at room temperature. The suspension was drained, and the resin was rinsed with DMF (3 ×), THF (5 ×), and CH_2Cl_2 (6 ×). Cleavage of the resin-bound boronic acid using the standard conditions described above, followed by concentration of the filtrates afforded **26d** as a white solid (16 mg, 81%)

3-(3'-Phenylpropyl-1'-amino)carbonylphenylboronic acid (26a)

White solid (60% yield by mass): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 8.16 (s, 1H), 7.88 (d, *J* = 7 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.28-7.11 (m, 5H), 3.40 (t, *J* = 7 Hz, 2H), 2.69 (t, *J* = 7 Hz, 2H), 1.93 (quintet, *J* = 7 Hz, 2H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 170.9, 143.1, 137.9, 135.0, 133.6, 129.9, 129.4, 129.4 128.7, 126.9, 40.8, 34.4, 32.3; IR (microscope) 3303, 3026, 2925, 1633, 1537 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{16}H_{19}BNO_3$ $(M+H)^+$ 284.1452, found 284.1452.

3-*iso*-Propylaminocarbonylphenylboronic acid (26b)

Off-white solid (56% yield by mass; 63% yield by ^{1}H NMR with 2,5-dimethylfuran internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 8.15 (s, 1H), 7.87 (d, *J* = 7 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 4.20 (septet, *J* = 7 Hz, 1H), 1.25 (d, *J* = 7 Hz, 6H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 170.1, 137.8, 135.3, 133.6, 130.0, 128.7, 43.1, 22.6; IR (microscope) 3335, 2976, 1621, 1536 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{10}H_{15}BNO_3$ $(M+H)^+$ 208.1139, found 208.1143.

3-*n*-Butylaminocarbonylphenylboronic acid (26c)

White solid (56% yield by mass; 55% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 8.16 (s, 1H), 7.88 (d, *J* = 7 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 3.37 (t, *J* = 7 Hz, 2H), 1.65-1-55 (m, 2H), 1.47-1.35 (m, 2H), 0.96 (t, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 170.8, 137.9, 135.1, 133.5, 129.9, 128.7, 40.7, 32.6, 21.2, 14.1; IR (microscope) 3310,

2954, 1637, 1536 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{17}BNO_3$ $(M+H)^+$ 222.1296, found 122.1297.

3-Phenylaminocarbonylphenylboronic acid (26d)

White solid (81% yield by mass; 83% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 8.29 (s, 1H), 7.95-7.92 (m, 2H), 7.69-7.65 (m, 2H), 7.47 (t, *J* = 8 Hz, 1H), 7.39-7.32 (m, 2H), 7.17-7.11 (m, 1H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 169.5, 139.8, 138.3, 135.5, 134.0, 130.3, 129.8, 128.8, 125.7, 122.3; IR (microscope) 3309, 3057, 1644, 1538 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{13}H_{13}BNO_3$ $(M+H)^+$ 242.0983, found 242.0980.

3-(Diethylamino)carbonylphenylboronic acid (26e)

White solid (77% yield by mass; 77% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.81 (d, *J* = 7 Hz, 1H), 7.71 (s, 1H), 7.44-7.36 (m, 2H), 3.57-3.51 (m, 2H), 3.31-3.25 (m, 2H), 1.27-1.22 (m, 3H), 1.12-1.07 (m, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 174.1, 137.2, 136.0, 132.4, 128.8, 128.8, 45.0, 40.8, 14.3, 13.1; IR (microscope) 3314, 3065, 2979, 2475, 1587 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{17}BNO_3$ $(M+H)^+$ 222.1296, found 222.1298.

3-(Di-*n*-butylamino)carbonylphenylboronic acid (26f)

Clear, colorless gum (77% yield by mass; 81% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.82 (d, *J* = 7 Hz, 1H), 7.71 (s, 1H), 7.44-7.35 (m, 2H), 3.50 (t, *J* = 7 Hz, 2H), 3.23 (t, *J* = 7 Hz, 2H), 1.71-1.62

(m, 2H), 1.55-1.36 (m, 4H), 1.17-1.05 (m, 2H), 0.99 (t, J = 7 Hz, 3H), 0.75 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 174.5, 137.2, 135.9, 132.6, 129.1, 128.8, 50.3, 46.0, 31.7, 30.7, 21.2, 20.6, 14.2, 13.8; IR (microscope) 3362, 2961, 1610, 1416, 1344 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{15}H_{25}BNO_3$ $(M+H)^+$ 278.1922, found 278.1930.

3-(Dibenzylamino)carbonylphenylboronic acid (26g)

White solid (61% yield by mass; 59% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.86-7.84 (m, 2H), 7.50-7.47 (m, 1H), 7.41-7.30 (m, 9H), 7.11-7.09 (m, 2H), 4.66 (s, 2H), 4.41 (s, 2H); ^{13}C NMR (125 MHz, 5% D_2O in CD_3OD) δ 175.1, 137.9, 137.4, 136.4, 136.3, 132.9, 129.9, 129.8, 129.2, 128.9, 128.8, 128.7, 128.3, 53.3; IR (microscope) 3364, 3030, 2926, 1606 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{21}H_{21}BNO_3$ $(M+H)^+$ 346.1609, found 346.1599.

4-(3'-Phenylpropyl-1'-amino)carbonylphenylboronic acid (27a)

White solid (64% yield by mass; 65% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.80 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.28-7.10 (m, 5H), 3.39 (t, J = 7 Hz, 2H), 2.72-2.64 (m, 2H), 1.92 (quintet, J = 7 Hz, 2H); ^{13}C NMR (125 MHz, 5% D_2O in CD_3OD) δ 170.5, 143.0, 137.1, 134.9, 129.4, 127.2, 126.9, 40.9, 34.5, 32.4; IR (microscope) 3310, 2924, 1633, 1545 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{16}H_{19}BNO_3$ $(M+H)^+$ 284.1458, found 284.1456.

4-*iso*-Propylaminocarbonylphenylboronic acid (27b)

Off-white solid (82% yield by mass; 80% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.81-7.72 (m, 4H), 3.18 (septet, J = 7 Hz, 1H), 1.24 (d, J = 7 Hz, 6H); ^{13}C NMR (125 MHz, 5% D_2O in CD_3OD) δ 169.7, 137.3, 134.8, 127.2, 43.3, 22.7; IR (microscope) 3239, 2972, 1633, 1548 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{10}H_{15}BNO_3$ $(M+H)^+$ 208.1139, found 208.1140.

4-*n*-Butylaminocarbonylphenylboronic acid (27c)

White solid (63% yield by mass): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.81 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H), 3.37 (t, J = 7 Hz, 2H), 1.65-1.55 (m, 2H), 1.47-1.34 (m, 2H), 0.96 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 170.5, 137.1, 134.9, 127.2, 40.8, 32.6, 21.2, 14.1; IR (microscope) 3257, 2958, 1634, 1546 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{17}BNO_3$ $(M+H)^+$ 222.1296, found 222.1303.

4-Phenylaminocarbonylphenylboronic acid (27d)

White solid (67% yield by mass): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.87 (s, 4H), 7.69-7.65 (m, 2H), 7.39-7.32 (m, 2H), 7.17-7.12 (m, 1H); ^{13}C NMR (100 MHz, 5% D_2O in CD_3OD) δ 169.1, 139.7, 137.6, 135.0, 129.8, 127.6, 125.7, 122.4; IR (microscope) 3301, 3042, 1643, 1537 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{13}H_{13}BNO_3$ $(M+H)^+$ 242.0983, found 242.0984.

4-(Diethylamino)carbonylphenylboronic acid (27e)

Yellow gum (59% yield by mass): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.81 (d, *J* = 7 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 3.53 (q, *J* = 7 Hz, 2H), 3.27 (q, *J* = 7 Hz, 2H), 1.24 (t, *J* = 7 Hz, 3H), 1.10 (t, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 173.8, 139.5, 135.1, 126.2, 44.9, 40.8, 14.4, 13.1; IR (microscope) 3380, 2974, 1598, 1549 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{11}H_{17}BNO_3$ $(M+H)^+$ 222.1296, found 222.1298.

4-(Di-*n*-butylamino)carbonylphenylboronic acid (27f)

White solid (57% yield by mass; 50% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.80 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 3.49 (t, *J* = 8 Hz, 2H), 3.22 (t, *J* = 8 Hz, 2H), 1.71-1.61 (m, 2H), 1.54-1.34 (m, 4H), 1.17-1.05 (m, 2H), 0.99 (t, *J* = 7 Hz, 3H), 0.75 (t, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 174.2, 139.6, 135.1, 126.4, 50.2, 45.9, 31.7, 30.7, 21.2, 20.7, 14.2, 13.8; IR (microscope) 3276, 2958, 1603, 1514 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{15}H_{25}BNO_3$ $(M+H)^+$ 278.1922, found 278.1928.

4-(Dibenzylamino)carbonylphenylboronic acid (27g)

White solid (69% yield by mass; 70% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.79 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 7.34-7.30 (m, 8H), 7.13-7.11 (m, 2H), 4.67 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.8, 138.0, 137.5, 135.1, 129.9, 129.2, 128.8, 128.2, 126.6, 53.1; IR

(microscope) 3357, 2918, 1605, 1341 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{21}H_{21}BNO_3$ $(M+H)^+$ 346.1609, found 346.1608.

4-[2'-(Diethylamino)ethylamino]carbonylphenylboronic acid (27h)

White solid (71% yield by mass; 70% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.80-7.70 (m, 4H), 3.56 (t, J = 7 Hz, 2H), 2.89 (t, J = 7 Hz, 2H), 2.82 (q, J = 7 Hz, 4H), 1.15 (t, J = 7 Hz, 6H); ^{13}C NMR (125 MHz, 5% D_2O in CD_3OD) δ 171.0, 134.9, 127.0, 52.6, 48.4, 37.8, 11.0; IR (microscope) 3326, 2970, 2820, 1638, 1543, 1432 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{13}H_{22}BN_2O_3$ $(M+H)^+$ 265.1718, found 265.1718.

2.6 References

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Chapter 3

Synthesis of *E*-Alkenylboronic Acids

3.1 Introduction

As mentioned in the preceding chapter, the amorphous nature of boronic acids, their amphiphilic character, and their instability towards silica gel chromatography make them difficult to handle and to purify. Despite the development of a large number of reagents for the synthesis of alkenylboronic acid derivatives (*vide infra*), a general and practical solution to the synthesis and purification of *free* boronic acids is still not available. As part of our program involving the cycloaddition of alkenylboronates with nitrile oxides (see Chapter 5), we required an efficient and reliable way to access functionalized alkenylboronic acids. In view of the problems associated with the existing methods, we set out to explore new ways of accessing this class of compounds.

Some useful organic transformations, such as the borono-Mannich reaction,[1] the rhodium(I)-catalyzed addition to aldehydes,[2] and the copper diacetate-promoted cross-coupling reactions involving amines, alcohols,[3] and thiols,[4] require the use of free, unprotected boronic acids. Whereas both aryl- and alkenylboronic acids can participate in these reactions, the challenges posed by the preparation and isolation of alkenylboronic acids has significantly hampered their use as compared to arylboronic acids. Indeed,

although some boronic esters can be purified with ease, distillation and chromatographic methods are generally unsuitable for the purification of alkenylboronic acids.

Over the years, numerous hydroboration reagents have been developed for the transformation of alkynes into alkenylboronic acids and their derivatives. Among the most commonly used ones are disiamylborane,[5] thexylborane,[5] dicyclohexylborane,[5] 9-BBN,[6] catecholborane,[7] di(isopropylprenyl)borane,[8] and dibromoborane[9] (Figure 3-1).

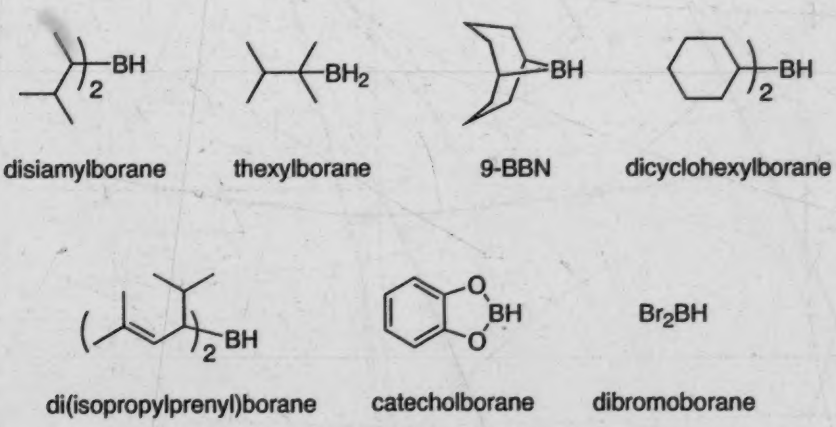
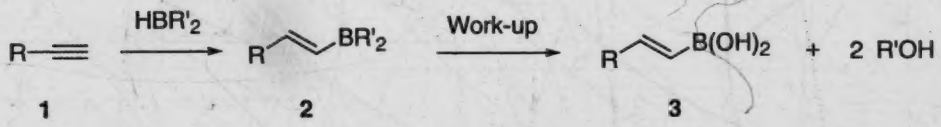


Figure 3-1. Common hydroboration reagents

When alkynes (**1**) are reacted with one of these boranes, an alkenylboronic acid (**3**) can be obtained following an appropriate work-up (Scheme 3-1). However, purification of the product can prove very troublesome. All the reagents cited above (except for dibromoborane) give rise to either an alcohol or a diol side-product. Unfortunately, this side-product has a high boiling point and tends to condense with the boronic acid during concentration, giving a boronic ester. For this reason, the product of the hydroboration reaction tends to be isolated as the boronic ester instead of the acid.

Dibromoborane does not suffer from this drawback, as there is no alcohol byproduct from this reaction. However, it is a very powerful reagent and it has a tendency to react with a wide range of other functional groups to yield undesired products. Moreover, catecholborane,[7] the current reagent of choice to access alkenylboronic acids through hydroboration, does not tolerate acetal or ether functionalities at the propargylic carbon. Also, hydrolysis of the boronate following catecholboration yields an equimolar amount of acidic catechol, which must be removed by recrystallization in water. In our hands, this isolation method proved difficult and not always reliable.



1 2 3

Scheme 3-1

Diisopinocampheylborane[10] (Figure 3-2) is a mild reagent that has been used extensively in the asymmetric hydroboration of alkenes. However, it has not received as much attention in the hydroboration of alkynes.[11] A particular feature that attracted our attention towards this reagent is the fact that no diol side-product is generated in the work-up of this reaction. This aspect potentially makes the isolation and purification of the alkenylboronic acid products much easier than for the other hydroboration reagents mentioned. As is described in this chapter, a system using diisopinocampheylborane was successfully applied to the synthesis of various functionalized alkenylboronic acids.

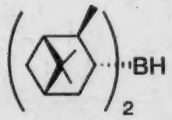
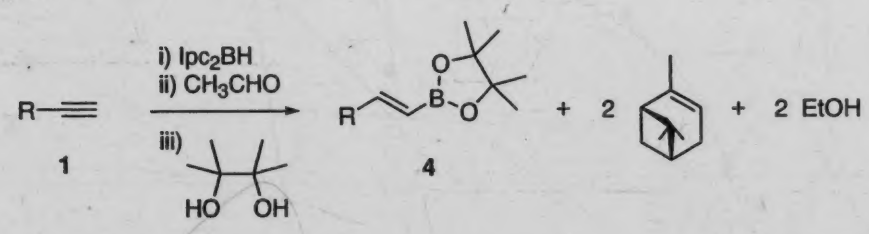


Figure 3-2. Structure of diisopinocampheylborane ($(Ipc)_2BH$)

3.2 Synthesis of alkenylboronic acids using diisopinocampheylborane

The mildness and selectivity of alkene hydroborations using diisopinocampheylborane[10] attracted us to using this method for alkyne hydroboration (Scheme 3-2). Typically, the alkyne (**1**) is hydroborated and then subjected to oxidative dealkylation using acetaldehyde, to afford a diethylboronate along with two equivalents of pinene. The boronic ester is then transesterified with pinacol to yield the pinacol ester (**4**), which, in some cases, can be purified by distillation or chromatography.[11] Because the *in situ* hydrolysis of the diethyl ester intermediate generates ethanol and pinene as the main side products, we reasoned that a general solvent system could be found to purify the boronic acids by simple extractions.



Scheme 3-2

Various alkynes (**1**) were subjected to a standard protocol consisting of hydroboration with diisopinocampheylborane, followed by treatment with acetaldehyde, hydrolysis and extraction of the reaction mixture using ethyl acetate (Table 3-1). We found that the poorly soluble boronic acids (**3**) could be easily purified by concentration of the ethyl acetate solution, followed by trituration of the precipitate with hexanes. The latter operation eliminated all residual pinene and afforded the corresponding boronic acids (**3a-j**) in good to excellent yield and in high purity.

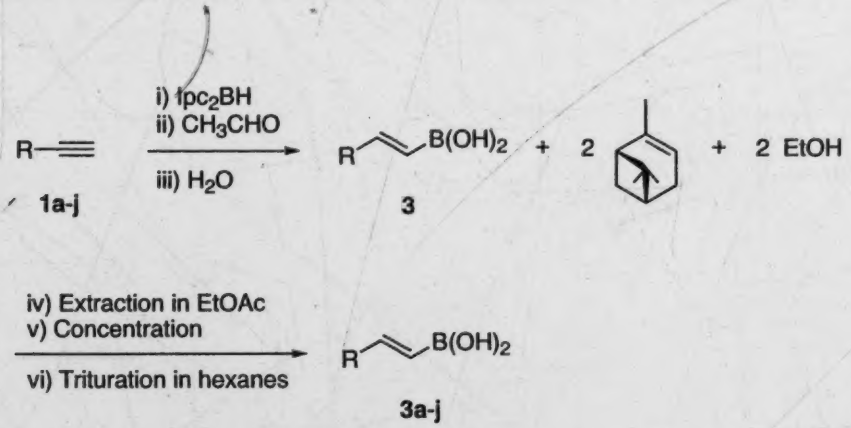
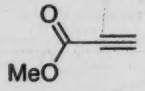
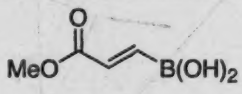
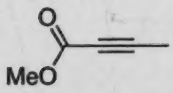
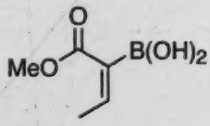
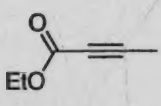
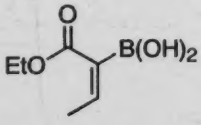
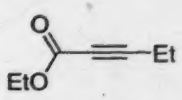
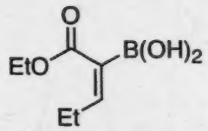
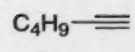
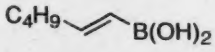
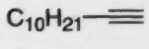
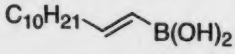
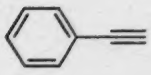
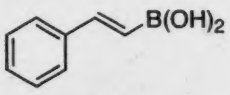
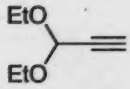
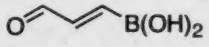
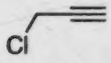
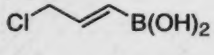
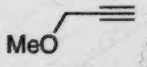
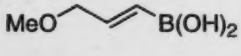


Table 3-1. Synthesis and purification of alkenylboronic acids

entry	alkyne	product[a]	yield (%)[b]
1	 **1b**	 **3a**	70
2	 **1b**	 **3b**	49
3	 **1c**	 **3c**	64

4	 **1d**	 **3d**	62
5	 **1e**	 **3e**	51
6	 **1f**	 **3f**	61
7	 **1g**	 **3g**	80
8[c]	 **1h**	 **3h**	84
9[c]	 **1i**	 **3i**	51
10[c]	 **1j**	 **3j**	84

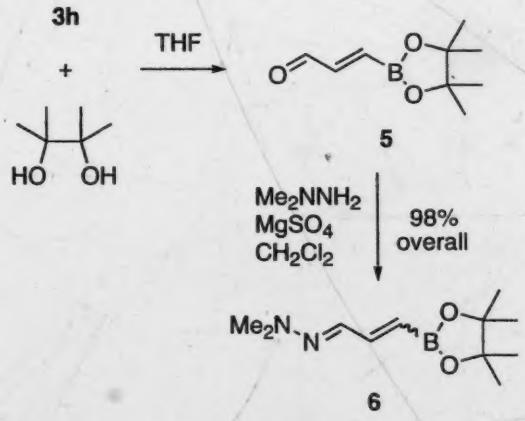
[a] Products isolated as a mixture of the free boronic acid and the corresponding boronic anhydride. [b] Yield of isolated, analytically pure product. [c] Result obtained by Barry Touré.

All products were obtained as air-stable white solids, and ^{1}H NMR analysis of the isolated boronic acids indicated the presence of a single regioisomer. Interestingly, we observed a complete reversal of regioselectivity between entries 1 and 2, indicating a competition between steric and electronic factors in the hydroboration of these alkynoates. This simple isolation procedure allowed the preparation of functionalized

alkenylboronic acids such as **3h-3j**. It is noteworthy that 3-borono-acrolein (**3h**) was obtained directly as the free aldehyde, following *in situ* hydrolysis of the diethyl acetal.

3.3 Synthesis of alkenylboronic esters

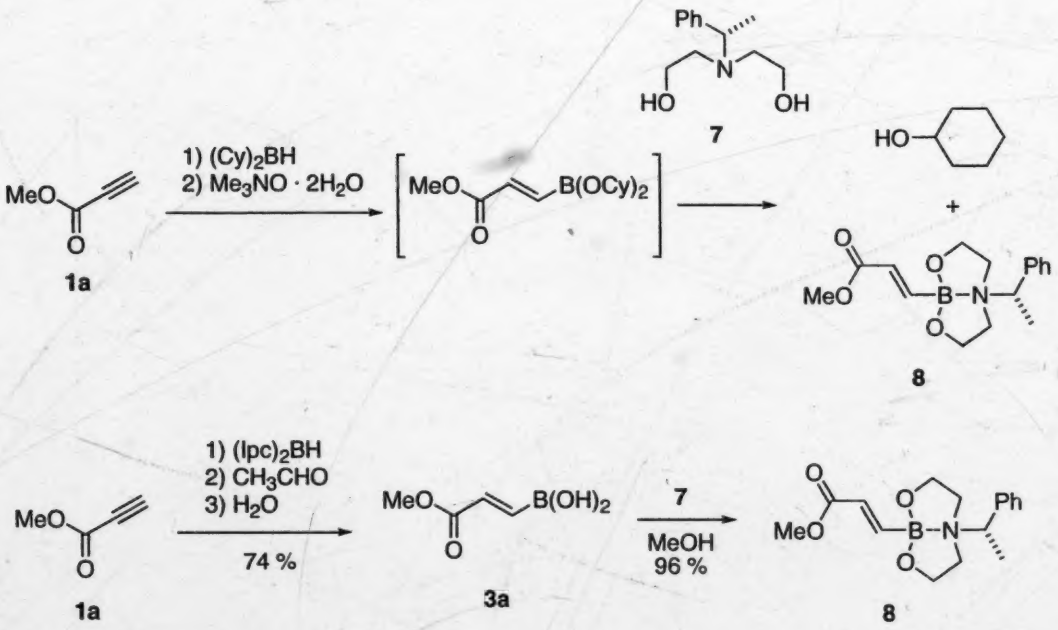
This approach greatly facilitates access to various alkenylboronates following protection of the boronic acid moiety (Scheme 3-3). For example, boronodiene **6** is easily obtained in pure form by condensation of boronic acid **3h** with pinacol, followed by condensation with *N,N*-dimethylhydrazine, without the need for any distillation or chromatographic purification.



Scheme 3-3

Another interesting example is shown in Scheme 3-4. The boronic acid-diethanolamine adduct **8** was first prepared by hydroboration of the corresponding alkyne **1a** using dicyclohexylborane, followed by oxidation and condensation with diethanolamine derivative **7**. However, the resulting product proved very difficult to

crystallize and it remained contaminated by substantial amounts of cyclohexanol. When pure alkenylboronic acid **3a** – obtained from our precedure – was used in the condensation reaction, the water generated in the process was easily removed under vacuum and the pure product **8** was obtained (see Chapter 6).



Scheme 3-4

In conclusion, we have developed a convenient isolation procedure to facilitate the preparation of *E*-alkenylboronic acids of high purity. The new protocol gives direct access to various functionalized alkenylboronic acids through an efficient work-up procedure featuring an extraction in ethyl acetate followed by a high-yielding trituration in hexanes. This method makes available alkenylboronic acids which are not readily accessible by other routes.

3.4 Experimental

3.4.1 General

All reactions were run under an argon atmosphere. Dried tetrahydrofuran was obtained by distillation over sodium/benzophenone ketyl. Commercially available alkynes were bulb-to-bulb distilled prior to use in the hydroboration reactions. NMR spectra were recorded on Bruker AM 300, Bruker AM 200, Varian i300, Varian i400, or Varian i500 MHz instruments. Due to their very low intensity, ^{13}C signals arising from the carbon bearing the boronic acid group were usually missing and were therefore not listed. Electrospray mass spectrometry was performed using Hewlett-Packard 1100 and ZabSpecETOF systems. Electron impact mass spectrometry was performed using a Kratos MS-50 instrument. A 1:1 mixture of MeCN/H_2O was used as the solvent for mass spectral analysis of boronic acids. It was important not to use an alcohol as solvent for the mass spectral analysis of boronic acids in order to avoid observing their corresponding boronate esters. Fourier-transform infrared spectroscopy was performed on a Nicolet 750 Magna instrument. Melting points were determined using a Gallenkamp apparatus. Compounds **3h-3j**, **5**, and **6** were prepared by Barry Touré and, therefore, their characterization data are not listed in this thesis.

3.4.2 Preparation of *E*-alkenylboronic acids 3a-j

(*R*)-(+)-α-Pinene (91% ee, 3.18 mL, 20 mmol) was slowly added to a solution of borane-dimethyl sulfide complex (1.00 mL, 10 mmol) in THF (2 mL) at 0 °C. The solution was warmed to room temperature and stirred for two hours. The resulting thick

white suspension was cooled to –40 °C and the alkyne (10 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 24 hours, although the reaction was generally over within 4 hours. The resulting solution was cooled to 0 °C and freshly distilled acetaldehyde (8 mL) was slowly added. The mixture was then refluxed for 16 hours at 45 °C, then water (15 mL) was added at 0 °C. The biphasic mixture was vigorously stirred for 1 hour and the top organic layer was decanted. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), then the organic layers were combined and concentrated to dryness under reduced pressure. The resulting suspension was then triturated in cold hexanes and filtered to yield the boronic acid **3** as a white solid. A second crop could be obtained by concentration of the filtrate and trituration in cold hexanes. If the product was still coloured, it could be washed with cold dichloromethane.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid (3a)

White solid (70%), mp 121-128 °C. ^{1}H NMR (500 MHz, CD_3OD + 5% D_2O) δ 6.78 (d, J = 17.9 Hz, 1H), 6.48 (d, J = 18.1 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD + 5% D_2O) δ 168.6, 136.3, 52.4; FTIR (microscope) 3427, 3321, 2953, 1706 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_4H_7O_4B$ 130.0437 found 130.0438.

(Z)-1-(Methoxycarbonyl)-2-methylvinylboronic acid (3b)

White solid (49%), mp 89-93 °C. ^{1}H NMR (400 MHz, CD_3OD + 5% D_2O) δ 6.90-6.70 (m, 1H), 3.72 (s, 3H), 1.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD +

5% D_2O) δ 173.0, 151.5, 131.3, 51.9, 17.4; FTIR (microscope) 3369, 3223, 2956, 1661 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_5H_9O_4B$ 144.0594 found 144.0595.

(Z)-1-(Ethoxycarbonyl)-2-methylvinylboronic acid (3c)

White solid (64%), mp 90-94 °C. ^1H NMR (400 MHz, CD_3OD + 5% D_2O) δ 6.90-6.70 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.92 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD + 5% D_2O) δ 172.8, 151.1, 61.7, 17.4, 14.6; FTIR (microscope) 3294, 3004, 2986, 1670 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_6H_{11}O_4B$ 158.0750 found 158.0752.

(Z)-1-(Ethoxycarbonyl)-2-ethylvinylboronic acid (3d)

White solid (62%), mp 63-67 °C. ^1H NMR (300 MHz, CD_3OD + 5% D_2O) δ 6.80-6.56 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.34 (q, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O) δ 172.6, 158.5, 157.2, 61.6, 25.5, 14.6, 13.6; FTIR (microscope) 3379, 3259, 2977, 1665, 1328 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_7H_{13}O_4B$ 172.0907 found 172.0909.

(*E*)-1-Hexenylboronic acid (3e)[9,12]

White solid (51%), mp 104-110 °C. ^1H NMR (300 MHz, CD_3OD + 5% D_2O) δ 6.57-6.40 (m, 1H), 5.34 (d, *J* = 17.8 Hz, 1H), 2.19-2.06 (m, 2H), 1.45-1.25 (m, 4H) 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD + 5% D_2O) δ 152.5, 124.1, 36.4, 31.9, 23.2, 14.3; FTIR (microscope) 3178, 2929, 1638 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_6H_{13}O_2B$ 128.1009 found 128.1011.

(*E*)-1-Dodecenylboronic acid (3f)

White solid (61%), mp 84-90 °C. ^{1}H NMR (500 MHz, CD_3OD + 5% D_2O) δ 6.55-6.43 (m, 1H), 5.35 (dt, J = 17.9, 1.4 Hz, 1H), 2.17-2.08 (m, 2H), 1.44-1.36 (m, 2H), 1.34-1.24 (m, 14H) 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O) δ 152.5, 36.9, 36.7, 33.0, 30.7, 30.6, 30.4, 30.3, 29.7, 23.7, 14.4; FTIR (microscope) 3457, 3334, 2922, 2848 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{12}H_{25}O_2B$ 212.1948 found 212.1950.

(*E*)-2-Phenylvinylboronic acid (3g)[13,14]

White solid (80%), mp 145-148 °C. ^{1}H-NMR (400MHz, CD_3OD + 5% D_2O) δ 7.50-7.45 (m, 2H), 7.34-7.22 (m, 4H), 6.15 (d, J = 13.5 Hz, 1H); ^{13}C (100 MHz, CD_3OD + 5% D_2O) δ 148.3, 148.2, 139.1, 129.6, 127.9; FTIR (film cast) 3020, 1615, 1574, 1493, 1438 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_8H_9O_2B$ 148.0696 found 148.0699.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid – *N*-[(1*S*)-(1-Phenyl)ethyl]diethanolamine adduct (8)

The preparation of this compound is described in Chapter 6.

3.5 References

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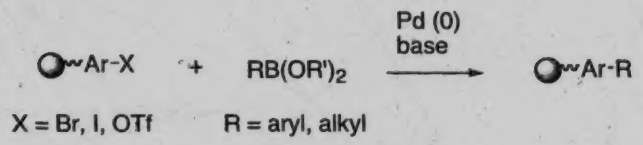
Chapter 4

Resin-to-Resin Suzuki Couplings

4.1 Introduction

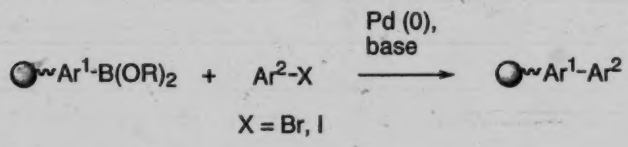
The application of the Suzuki reaction to solid phase chemistry has attracted a lot of attention over the past 10 years.[1] This level of interest can be explained by the possibility of generating complex structures from simple starting materials through a carbon-carbon bond formation. Moreover, the Suzuki reaction is known for its reliability as it tolerates a wide range of functional groups. This general tolerance for functional groups along with its synthetic usefulness makes the Suzuki coupling an ideal reaction for use in combinatorial chemistry, as libraries of highly functionalized and complex structures can be accessed in a straightforward fashion using solid phase methods.

Most strategies employed so far have relied on the attachment of the halide coupling partner onto a solid support (Scheme 4-1),[1] with the boronic acid or ester counterpart present in the solution phase. This preference can be explained by the wider availability of halide compounds that can be easily linked to, or synthesized on a solid support. Indeed, the vast majority of boronates used in the subsequent Suzuki coupling reactions are simple, commercially available boronic acids.



Scheme 4-1

The reverse situation – a resin-bound boronate and the halide in solution – has also been studied, although to a lesser extent (Scheme 4-2).[1] The arylboronates used in this process are again relatively simple and thus generate coupled products of limited complexity.

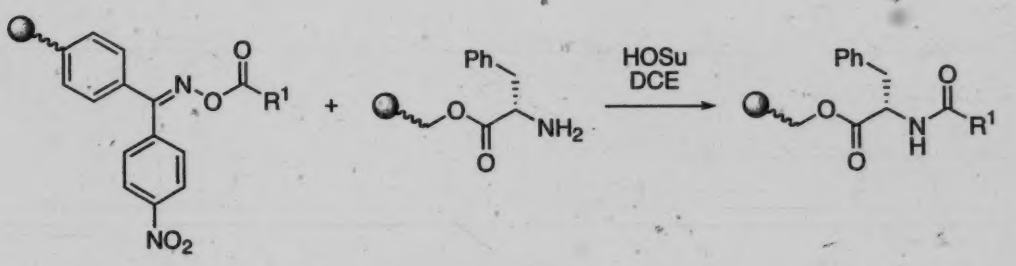


Scheme 4-2

With the development of the DEAM-PS resin by our group, a wide variety of functionalized arylboronic acids became readily available. The use of these newly accessible boronic acids in Suzuki coupling reactions allows the synthesis of highly functionalized products that could not be generated efficiently using earlier solid phase strategies. Moreover, the direct coupling of solid-supported arylboronic acids to solid-supported aryl halides would represent a highly convergent approach to multifunctionalized biphenyl units. This strategy featuring a key Suzuki resin-to-resin transfer reaction (RRTR), is presented in this chapter.

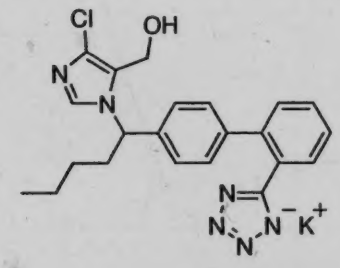
4.2 Background on resin-to-resin transfer reactions (RRTR)

In comparison with the traditional approach to solid-phase synthesis where a single resin-bound substrate is employed, the simultaneous use of two or more heterogeneous substrates, reagents or catalysts has seldom found real synthetic utility. Resin-to-resin transfer reactions (RRTR) constitute a type of multi-resin system that further simplifies the practice of solid-phase organic synthesis (SPOS). In RRTR systems, a resin-bound substrate is transferred to the solution phase by the action of a phase-transfer agent (also known as a chaperone) and then coupled *in situ* to another resin-bound substrate. This concept allows for the convergent solid-phase synthesis and eventual coupling of fragments for which a linear SPOS strategy would involve incompatible reaction conditions. Although RRTR was first used in the 1970's as a tool for the study of reaction mechanisms,[2] it was used for synthetic purposes for the first time only in 1999 by DeGrado and coworkers.[3] Their system involved the transfer acylation and aminoacylation of oxime resin-bound substrates onto Wang resin-linked phenylalanine, using *N*-hydroxysuccinimide as the chaperone (Scheme 4-3).

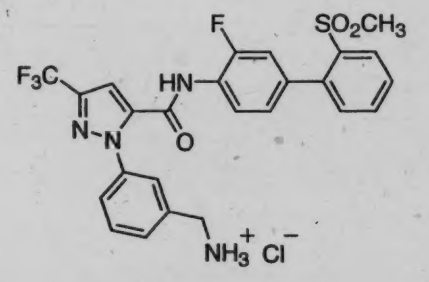


Scheme 4-3

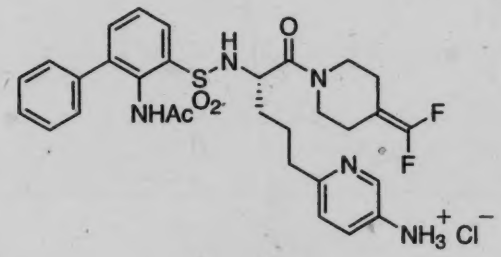
We believed that interesting synthetic applications of RRTR could arise using our newly developed DEAM-PS resin. Specifically, we envisaged a Suzuki RRTR strategy that would give us access to unsymmetrically functionalized biphenyl units, a structural motif found in several biologically active molecules (Figure 4-1).[4]



DuP 753
Angiotensin II recepor antagonist



DPC423
Blood coagulation factor Xa inhibitor



SSR182289A
Thrombin inhibitor

Figure 4-1. Biologically active biphenyl-containing compounds

4.3 Use of DEAM-PS in RRTR systems

In combinatorial chemistry, the concept of RRTR could find applications for the construction of new product libraries where each resin-bound substrate can be a member of a respective library assembled by solid-phase synthesis. As seen in Chapter 2, DEAM-PS resin facilitates the synthesis of functionalized arylboronic acids that can otherwise be difficult to isolate and handle in solution. Their direct use with another resin-bound substrate in RRTR processes could eliminate time-consuming cleavage and transfer operations, thereby considerably simplifying the synthesis of combinatorial libraries by manual or automated means. The use of DEAM-PS-supported boronic acids also facilitates the transfer of small quantities of boronic acid, and also circumvents their tendency to dehydrate, giving anhydrides that are difficult to weigh accurately.

Phase transfer in RRTR processes involving DEAM-PS boronate adducts could be promoted by exposure to water or alcohols under conditions that must be compatible with the desired reaction. Both the added phase-transfer agent and the released DEAM-PS resin must be inert to all reagents used in these processes. With these criteria in mind, we have designed a strategy for resin-to-resin Suzuki coupling reactions via phase transfer of DEAM-PS-supported arylboronic acids under both aqueous and anhydrous conditions.[5] The potential of these methods was demonstrated with the convergent solid-phase synthesis of compounds with unsymmetrically functionalized biphenyl units.

As shown conceptually in Figure 4-2, transesterification of the DEAM-PS-supported boronate **2** is expected to liberate the boronic acid in solution (as an ester), so that it can be transferred *in situ* to a haloarene resin under palladium catalysis and added base.

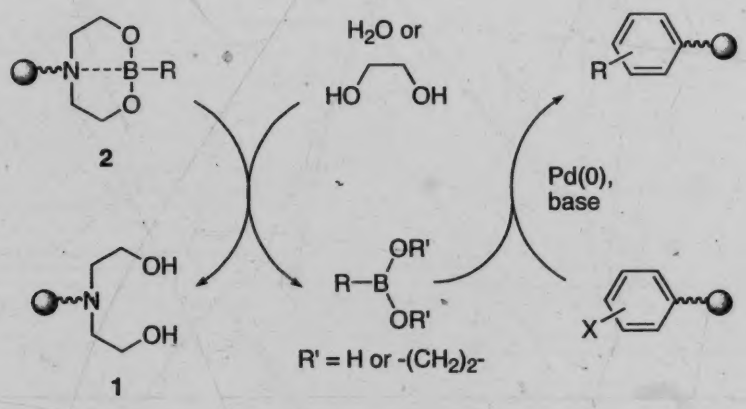
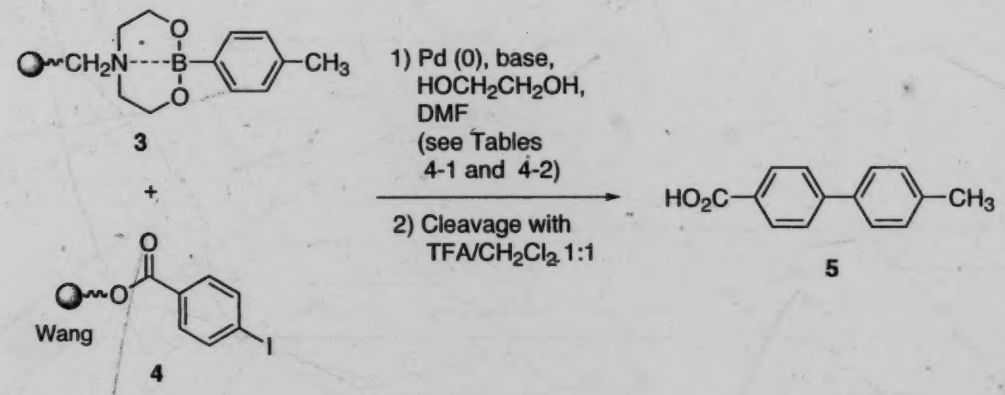


Figure 4-2. Resin-to-resin transfer Suzuki coupling

4.4 Optimization of Suzuki RRTR conditions

As a working model, the transfer of DEAM-PS-supported *p*-tolueneboronic acid (**3**) to Wang resin-bound *p*-iodobenzoic acid (**4**)[6] was attempted with different stoichiometries under various solvent, base, and temperature conditions (Scheme 4-4). The resulting resin mixture was then treated with 1:1 trifluoroacetic acid/dichloromethane to liberate the biphenyl product **5** and any unreacted *p*-iodobenzoic acid. Any DEAM-PS-bound boronic acid that fails to react can be rinsed off from the resin prior to cleavage of the coupling product by carrying out aqueous washes. The leftover

DEAM-PS resin does not liberate any by-products upon treatment with TFA. From these initial studies, we concluded that DMF as the solvent and excess ethylene glycol as the phase transfer agent provided optimal results.[5]



Scheme 4-4

Next, we explored the effect of the nature of the base on conversion using 50 mol% $Pd_2(dba)_3$ at 60 °C (Table 4-1). To this end, we found that only fluoride and triethylamine were satisfactory, and even provided biphenyl products at room temperature (entries 7 and 10).

Table 4-1. Anhydrous Suzuki RRTR of 3 and 4: Effect of Base and Temperature under $Pd_2(dba)_3$ Catalysis (50 mol%)[a]

entry	base	temperature (°C)	conversion (%)[b]	yield (%)[c]
1	NaOH	60	-	0[d]
2	$Ba(OH)_2$	60	-	0[d]
3	K_2CO_3	60	-	0[d]
4	Cs_2CO_3	60	-	0[d]
5	K_3PO_4	60	-	0[d]
6	KF	60	>98	>98
7	KF	25	78	74
8	CsF	60	>98	>98
9	Et_3N	60	>98	>98
10	Et_3N	25	72	71

[a] Typical trials were carried out with 20 mg of **4** (0.55 mmol g^{-1}) and **3** (3.2 equiv., 45 mg, 0.79 mmol g^{-1}) with the indicated base (10 equiv.) and 50 mol% $Pd_2(dba)_3$ as catalyst in DMF-ethylene glycol 10:1 (2.5 mL) for 18 h. [b] Measured by ^1H NMR integration of representative signals on crude reaction products. [c] Non optimized yields of crude products after cleavage from the resin and drying *in vacuo* for > 12 hours. The reported values are usually an average of mass balance and internal standardization (see section 4.7 for details). [d] Premature cleavage.

We then sought general optimal conditions that are sufficiently mild to minimize alcoholysis of the Wang ester linker while still providing complete coupling within 20 hours at 105 °C, with only 1.5 equivalents of DEAM-PS-supported boronic acid, and with a lower catalyst loading (Table 4-2). Triethylamine, when used as a co-solvent, was found to be the most effective base in combination with 20% $PdCl_2(dppf)$ as catalyst (entries 7-8). The latter was preferably added in 2-3 portions over a few hours to minimize the effects of catalyst inactivation. Interestingly, although the use of cesium fluoride and TBAF as bases led to full conversion, both led to low yields of biphenyl

product due to premature cleavage of the product at 105 °C (entries 2-3). This undesired cleavage most likely occurs by alcoholysis of the Wang ester linker with ethylene glycol. However, using KF or triethylamine as the base did not lead to premature cleavage of the product from the resin. Efforts to lower the effective temperature of reaction by using Buchwald's[7] or Fu's[8] ligand systems failed.

Table 4-2. Anhydrous Suzuki RRTR of 3 and 4: Effect of Base and Catalyst at High Temperature (105 °C)[a]

entry	base	catalyst	conversion (%)[b]	yield (%)[c]
1	NaF	$Pd_2(dba)_3$	29	33
2	TBAF	$Pd_2(dba)_3$	>98	<2
3	CsF	$Pd_2(dba)_3$	>98	3
4	KF	$Pd_2(dba)_3$	93	65
5	KF	$PdCl_2(dppf)$	>98	48
6	Et_3N[d]	$Pd_2(dba)_3$	42	58
7	Et_3N[d]	$PdCl_2(dppf)$	81	63
8	Et_3N[d]	$PdCl_2(dppf)$[e]	>98	64

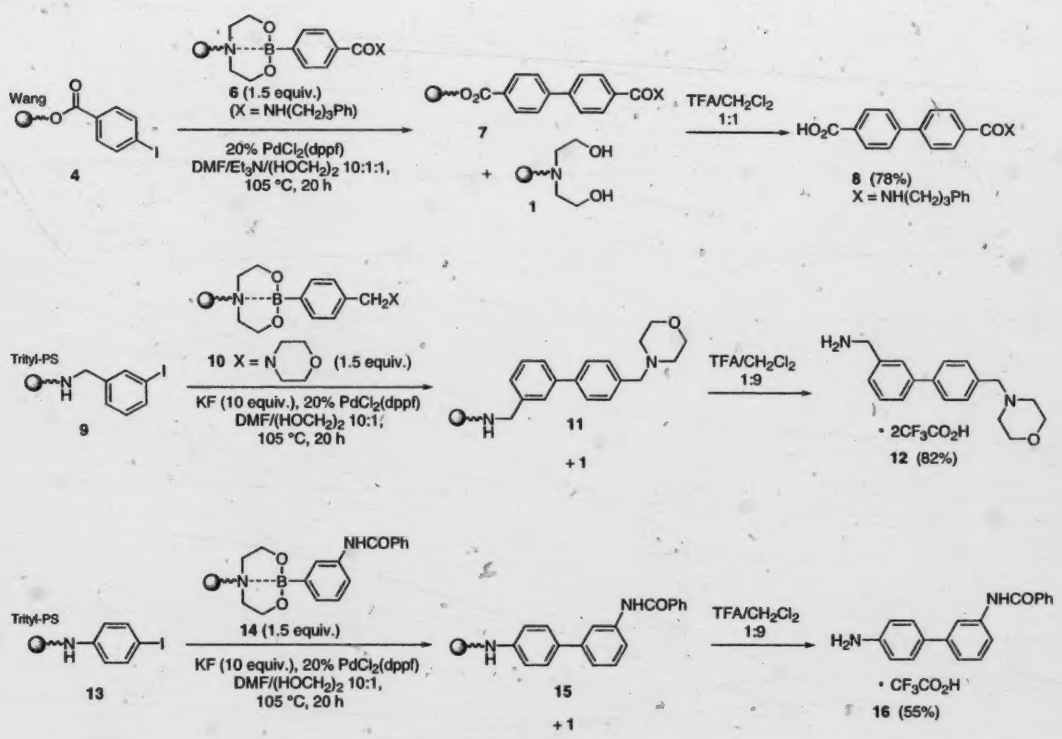
[a] Typical trials were carried out with 40 mg of **4** (0.98 mmol g^{-1}) and **3** (1.5 equiv., 58 mg, 1.07 mmol g^{-1}) with the indicated base (10 equiv.) and catalyst (10 mol% $Pd_2(dba)_3$ or 20 mol% $PdCl_2(dppf)$) in DMF-ethylene glycol 10:1 (2.5 mL) at 105 °C for 20 h. [b] Measured by ^1H NMR integration of representative signals on crude reaction products. [c] Non optimized yields of crude products after cleavage from the resin and drying *in vacuo* for > 12 hours. The reported values are based on internal standardization (see section 4.7 for details). [d] A large excess was used (0.25 mL). [e] The catalyst was added in two equal portions, one at the start, one after 8 h.

Control experiments were devised to confirm the role and efficiency of ethylene glycol as phase transfer agent. Resin-to-resin cross coupling of model substrates **3** and **4** in the absence of ethylene glycol gave largely incomplete transfer as shown by a lower than 50% conversion to product **5**. Similarly, treatment of DEAM-PS-supported

p-tolylboronic acid alone in hot anhydrous DMF/Et_3N (9:1, 105 °C, 24 h) led to less than 25% release of the boronic acid. These experiments confirmed the expected advantage of using the phase transfer agent. In fact, the rate at which ethylene glycol transesterifies the resin-bound boronic acid is much faster than the rate of the cross-coupling. When resin **3** was heated at 105 °C in an 8:1:1 mixture of DMF/triethylamine/ethylene glycol, less than 10% of the boronic acid remained bound to the DEAM-PS support after 30 minutes.

4.5 Application of Suzuki RRTR to convergent biphenyl synthesis

The usefulness of DEAM-PS to synthesize new arylboronic acids and the potential of the resin-to-resin Suzuki coupling strategy were clearly demonstrated by the convergent syntheses of unsymmetrically functionalized biphenyl compounds (Scheme 4-5). The DEAM-PS-supported amide derivative **6** was made as described in Chapter 2. Following washing and drying operations, it was reacted with **4** using the optimal conditions of Table 4-2, affording 4,4'-biphenyl dicarboxylic acid monoamide **8** after cleavage from the resin mixture (**7** + **1**). This example makes a very significant case for using a convergent RRTR strategy in solid-phase synthesis. Indeed, as *p*-carboxybenzeneboronic acid is inept as a substrate in Suzuki reactions,[9] a linear solid-phase strategy involving its coupling to **4** followed by amide formation would not be possible.



Scheme 4-5

The Suzuki RRTR strategy is also useful for providing monoalkylated biphenyl dibenzylamines. For example, DEAM-PS-bound *p*-(*N*-morpholinomethyl)benzeneboronic acid (**10**) was treated with trityl-PS bound *m*-iodobenzylamine (**9**) under a slightly modified RRTR method (using KF as base), and afforded crude diamine **12** in 82% yield and high purity (> 90% by ^{1}H NMR) after cleavage of the resin mixture. This example is significant because a linear synthesis based on the cross-coupling of **9** with *p*-(bromomethyl)benzeneboronic acid would be hampered by incompatible reaction conditions. The basic conditions required in the Suzuki coupling could promote nucleophilic displacement on the benzylic bromide that, in addition, can react slowly with

palladium(0) by oxidative addition. As shown through the isolation of **16**, monoacylated biphenyl dianilines can also be synthesized efficiently.

4.6 Application of Suzuki RRTR to combinatorial chemistry

In the above examples, cleavage and handling of the boronic acid prior to the Suzuki coupling was eliminated and there was no need to transfer the resin to a new reaction vessel after washing and drying operations. These advantages are very appealing for combinatorial chemistry applications in which libraries of new DEAM-PS-bound arylboronic acids could be made and combined with libraries of supported haloarenes. To demonstrate this concept, a small model library was made using a commercial, semi-automated parallel synthesizer (Scheme 4-6).[a] Supported boronic acids **19a-c** were synthesized from **17** and acid chlorides **18a-c**, and after resin rinsing were immediately reacted with iodoarene resins **9** and **13** under similar conditions used in the synthesis of **16**. After on-line cleavage, all six biphenyl products **20a-c** and **21a-c** were obtained in excellent yields (75-100%) and good purity (> 90% by NMR). Interestingly, reactions performed with the synthesizer were significantly more efficient and cleaner compared to the manual protocol (Scheme 4-5) using glass vessels. The higher purity of the automated process was clearly shown by comparing spectra of reference library member **21a** with another sample made previously via manual synthesis (see **16** in Scheme 4-5).

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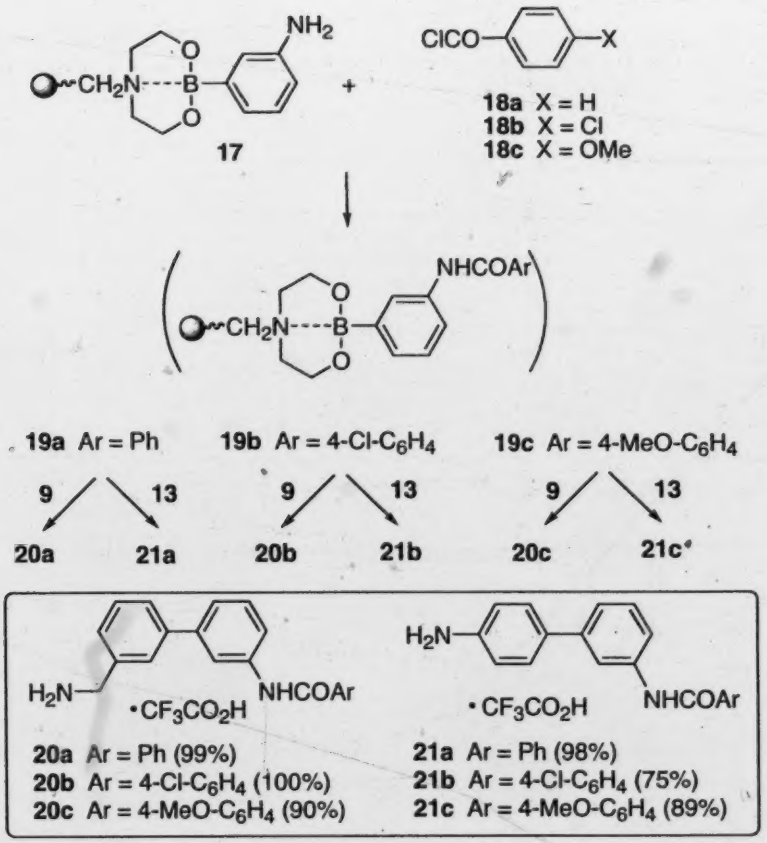
[a] A Quest 210 instrument with solvent wash unit was employed (Argonaut Technologies). Cleavage was effected on-line and crude products were obtained after evaporation of solvents. Yields and purity were estimated by comparison with an internal NMR standard.



Scheme 4-6

4.7 Conclusion

In summary, we have developed conditions for the resin-to-resin Suzuki coupling of DEAM-PS-supported boronic acid with haloarene resins. One of the main advantages of this method is to allow a convergent solid-phase synthesis and eventual coupling of fragments for which a linear SPOS strategy would involve incompatible reaction conditions. It also eliminates time-consuming cleavage and transfer operations, thereby

considerably simplifying the synthesis of combinatorial libraries by manual or automated means. Accordingly, a small model library was synthesized to illustrate the usefulness of the newly developed methodology.

4.8 Experimental

4.8.1 General

All starting boronic acids employed are commercially available (Lancaster, Frontier Scientific, and Combi-Blocks) and were used without purification. All other reagents are also commercially available and unless stated otherwise they were used without purification. Starting resins were purchased from Rapp-Polymere (Tübingen, Germany) and Nova-Biochem (La Jolla, California). In most cases, the loading value stated by the supplier was used. Solid-phase reactions that required heating were performed in glassware silanized by treatment with 20% TMSCl/toluene for >12 hours. Those done at room temperature were agitated inside polypropylene (pp) filter vessels purchased from Bio Rad (Hercules, California) and International Sorbent Technology Ltd. (Hengoed, UK). Resin washing operations were carried out on a vortexer. THF and Et_2O for reactions and cleavage (including resin washes) were dried by distillation over sodium/benzophenone ketyl and used the same day. Dichloromethane, toluene and methanol were distilled over calcium hydride. Anhydrous NMP and DMF were obtained commercially. DMF, ethylene glycol, and Et_3N were degassed prior to use in Suzuki resin-to-resin transfer reactions. ^1H NMR spectra were recorded at 300 or 500 MHz. Unless indicated otherwise, ethyl acetate was used as an internal standard in ^1H NMR,

and it was found to provide very consistent values under a 15 s relaxation delay. APT (Attached Proton Test) and BB (broad band) ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. Low resolution electrospray mass spectra were acquired using atmospheric pressure ionization (API) with a quadrupole mass analyser (positive mode). High-resolution (HRMS) and low-resolution mass spectrometry analyses were obtained on a time-of-flight instrument. FTIR spectra were acquired on a Nicolet Magna 750 FTIR Spectrometer and a Nic-Plan FTIR Microscope. For resin-to-resin transfer reactions, runs were done in 5 mL teflon fritted vessels on a Quest 210 instrument with solvent wash unit (Argonaut Technologies), or in a silanized round bottom flask fitted with a condenser.

4.8.2 Preparation of resins used in Suzuki RRTR's

Preparation of resins 3, 6, and 10

These resins were prepared according to the procedures for the derivatization of resin-bound boronic acids as described in Chapter 2. Instead of being cleaved, the resins were dried under high vacuum for > 24 h.

***N*-(Benzoyl)-3-aminophenylboronic acid-DEAM-PS adduct 14**

m-Aminobenzeneboronic acid was immobilized on DEAM-PS as described in Chapter 2. The resulting resin (102 mg, 0.097 mmol, theoretical loading: 0.95 mmol g^{-1}) was added to a 10 mL pp vessel and swollen in NMP (1.5 mL). PyBOP (100 mg, 0.19 mmol), DIPEA (67 μL, 0.39 mmol), and benzoic acid (23 mg, 0.19 mmol) were added sequentially and the reaction vessel was shaken for 19 hours at room temperature. The suspension was drained, and the resin was rinsed with NMP (3 ×), CH_2Cl_2 (5 ×), THF

(3 ×), and dried under high vacuum for > 24 h. A small sample was cleaved from the resin using the standard conditions described in Chapter 2:

***N*-(Benzoyl)-3-aminophenylboronic acid.** Beige solid (86% yield by mass; 77% yield by ^{1}H NMR with EtOAc int. std.): ^{1}H NMR (300 MHz, 5% D_2O in CD_3OD) δ 7.93-7.90 (m, 3 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.60-7.47 (m, 4 H), 7.34 (t, J = 7.7 Hz, 1 H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 169.0, 142.1 (broad), 138.9, 136.2, 132.9, 131.3, 129.7, 129.1, 128.6, 128.0, 124.7; FTIR (microscope) 3317, 3066, 3045, 1645, 1603, 1580 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{13}H_{13}BNO_3$ $(M+H)^+$ 242.0983, found 242.0984.

4-Iodobenzoate Wang-PS resin (4)

To a suspension of Wang resin (1.00 g, 0.63 mmol, theoretical loading: 0.63 mmol g^{-1}) in 10 mL of CH_2Cl_2 in a pp vessel were added successively 4-iodobenzoic acid (240 mg, 0.95 mmol), triethylamine (135 mL, 0.98 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (180 mg, 0.94 mmol), and HOBt·H_2O (15 mg, 0.098 mmol), vortexing after each addition. The suspension was shaken at room temperature for 24 hours, after which the resin was rinsed with DMF (5 ×), CH_2Cl_2 (5 ×), and dried under high vacuum for > 24 hours, affording 1.18 g of a white resin (theoretical: 1.14 g, 0.55 mmol g^{-1}).

3-Iodobenzylamino trityl-PS resin (9)

A solution of 3-iodobenzylamine (213 mL, 1.6 mmol) in 8 mL of CH_2Cl_2 was added to trityl chloride resin (500 mg, 0.40 mmol, theoretical loading: 0.80 mmol g^{-1}) in a pp vessel. The resulting suspension was shaken for 3 hours, after which the resin was

rinsed with CH_2Cl_2 (3 ×), 19:1 DMF/Et_3N (3 ×), MeOH (1 × (15 min.)), CH_2Cl_2 (5 ×), and dried under high vacuum for > 24 hours, affording 545 mg of a white resin (theoretical: 557 mg, 0.72 mmol g^{-1}).

4-Iodoanilino trityl-PS resin (13)

A solution of 4-iodoaniline (360 mg, 1.6 mmol) in 8 mL of pyridine was added to trityl chloride resin (1.03 g, 0.82 mmol, theoretical loading: 0.80 mmol g^{-1}) in a pp vessel. The resulting suspension was shaken for 3 days, after which the resin was rinsed with pyridine (4 ×), diethyl ether (5 ×), and dried under high vacuum for > 24 hours, affording 1.16 g of a white resin (theoretical: 1.18 g, 0.70 mmol g^{-1}).

4.8.3 Suzuki resin-to-resin transfer reactions

Typical procedure for the Suzuki RRTR using resin 4:

4'-Methyl-biphenyl-4-carboxylic acid (5)

To a mixture of DEAM-PS supported *p*-tolylboronic acid **3** (77 mg, 0.075 mmol, theoretical loading: 0.97 mmol g^{-1}) and 4-iodobenzoate Wang-PS resin **4** (49 mg, 0.050 mmol, theoretical loading: 1.02 mmol g^{-1}) in a 10-mL round-bottom flask were added successively DMF (2.5 mL), ethylene glycol (0.25 mL), triethylamine (0.25 mL), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (4 mg, 0.005 mmol). The flask was equipped with a reflux condenser and the suspension was stirred gently at 105 °C under a nitrogen flow. After 8 hours of heating, a second portion of $PdCl_2(dppf)\cdot CH_2Cl_2$ (4 mg, 0.005 mmol) was added. After heating for 12 hours, the reaction mixture was cooled to room temperature. The mixture was transferred to a pp vessel, and then rinsed successively with DMF (1 ×), 1:1

DMF/H_2O (3 ×), MeOH (3 ×), CH_2Cl_2 (6 ×). The resulting brown resin was swollen in CH_2Cl_2 (1 mL) and trifluoroacetic acid (1 mL), and the resulting suspension was stirred for 2 hours. The resin was filtered and rinsed with a 1:1 CH_2Cl_2/TFA solution (2 ×). The combined filtrates were concentrated and dried under high vacuum, affording a pale brown solid[b] (64% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (500 MHz, CD_3OD) δ 8.06 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, 5% D_2O in CD_3OD) δ 164.9, 147.0, 139.3, 138.3, 131.3, 130.7, 128.0, 127.7, 21.1; FTIR (microscope) 3300-2500, 3028, 2916, 1678, 1607, 1358 cm^{-1}; HRMS (EI, m/z) calcd for $C_{14}H_{12}O_2$ 212.0837, found 212.0838.

4'-(3-Phenylpropylcarbamoyl)-biphenyl-4-carboxylic acid (8)

Pale brown solid (78% yield by ^1H NMR with EtOAc internal standard): ^1H NMR (300 MHz, CD_3OD) δ 8.10 (d, J = 8.7 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H), 7.78 (m, 4H), 7.29-7.13 (m, 5H), 3.44 (t, J = 7 Hz, 2H), 2.71 (t, J = 8 Hz, 2H), 1.96 (tt, J = 8, 8 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD)[c] δ 170.6, 169.9, 145.3, 144.4, 143.1, 135.2, 131.4, 129.5, 129.0, 128.3, 128.1, 126.9, 40.8, 34.4, 32.3; FTIR (microscope) 3400-2400, 3343, 3298, 3031, 2928, 1679, 1626 cm^{-1}; HRMS (ES, m/z) calcd for $C_{23}H_{21}NNaO_3$ $(M+Na)^+$ 382.1419, found 382.1418.

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[b] Although analyses (^1H NMR, ^{13}C NMR, FTIR, HRMS) indicated pure products, the brown color revealed the presence of putative palladium species. These palladium impurities can be removed by preparative thin layer chromatography.

[c] The resolution of this ^{13}C NMR was poor because of the limited solubility of the product in most commercial deuterated solvents.

Typical procedure for the Suzuki RRTR using resins 9 and 13:

***C*-(4'-Morpholin-4-ylmethylbiphenyl-3-yl)-methylamine (12)**

To a mixture of DEAM-PS supported **10** (121 mg, 0.075 mmol, experimental loading: 0.62 mmol g^{-1}) and resin **9** (72 mg, 0.050 mmol, theoretical loading: 0.69 mmol g^{-1}) in a 10 mL teflon fritted reaction vessel were added successively DMF (2.5 mL), ethylene glycol (0.25 mL), potassium fluoride (29 mg, 0.50 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (7 mg, 0.010 mmol). The suspension was mixed at 105 °C for 20 hours under a nitrogen atmosphere and then cooled to room temperature. The mixture was filtered, and then rinsed with DMF (1 ×), 1:1 DMF/H_2O (3 ×), MeOH (3 ×), CH_2Cl_2 (6 ×). The resulting brown resin was swollen in CH_2Cl_2 (2 mL) and trifluoroacetic acid (0.2 mL), and the suspension was stirred for 2 hours. The resin was filtered and rinsed with a 10% TFA/CH_2Cl_2 solution (2 ×). The combined filtrates were concentrated and dried under high vacuum, affording a brown oil (82% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, CD_3OD) δ 7.80-7.40 (m, 8H), 4.40 (s, 2H), 4.19 (s, 2H), 4.01 (br s, 2H), 3.76 (br s, 2H), 3.37 (br s, 2H), 3.23 (br s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 143.5, 142.1, 135.3, 133.1, 130.9, 129.5, 129.3, 128.9, 128.8, 128.7, 65.0, 61.6, 52.9, 44.3; FTIR (MeOH cast) 3300-2400, 2996, 1675, 1203, 1132 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{18}H_{23}N_2O$ $(M+H)^+$ 283.1805, found 283.1820.

***N*-(4'-Aminobiphenyl-3-yl)-benzamide (16)**

Brown solid (55% yield by ^{1}H NMR with EtOAc internal standard): ^{1}H NMR (300 MHz, CD_3OD) δ 8.07 (s, 1H), 7.95 (d, J = 6.9 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.68-7.34 (m, 8H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.0, 141.9, 140.5, 136.2, 135.5, 133.0,

130.4, 129.7, 129.5, 128.6, 124.0, 122.7, 121.4, 120.7; FTIR (MeOH cast) 3500-2400, 2917, 2624, 1673, 1202 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{19}H_{17}N_2O$ $(M+H)^+$ 289.1335, found 289.1338.

4.8.4 Model library

Synthesis of amide resins 19a-c, using a Quest 210 instrument

m-Aminobenzeneboronic acid was immobilized on DEAM-PS as described in Chapter 2. To the resulting resin **17** (136 mg, 0.12 mmol, theoretical loading: 0.85 mmol/g) was added dry THF (2 mL) and diisopropylethylamine (223 μL, 1.28 mmol), and the mixture was vortexed for a few seconds. The aryl chloride **18a-c** (1.16 mmol) was then added dropwise in six portions, with vortexing in between. The resulting suspension was shaken mechanically for 16 hours, and then the resin was rinsed with dry THF (8 ×), and dried under a flow of argon to obtain a colorless resin (**19a-c**), which was used directly in the next step.

Synthesis of library members 20a-c and 21a-c using a Quest 210 instrument

Resin **19** (0.12 mmol) and iodoarene resin **9** (21 mg, 0.021 mmol, theoretical loading: 0.99 mmol g^{-1}) or **13** (20 mg, 0.019 mmol, theoretical loading: 0.97 mmol g^{-1}) were charged in a 5-mL reaction vessel and purged with nitrogen. To this mixture was added successively DMF (2.5 mL), ethylene glycol (0.25 mL), and potassium carbonate (20 mg, 0.15 mmol). The suspension was shaken for 10 seconds, then $Pd_2(dba)_3 \cdot CH_2Cl_2$ (3 mg, 0.003 mmol) was added. The suspension was shaken at 115 °C for 48 hours, additional DMF (2.5 mL) was introduced, and then shaking was continued at 115 °C for

another 24 hours. The mixture was cooled to room temperature, rinsed with DMF (1 ×), DMF/H_2O (1:1) (3 ×), MeOH (3 ×), and CH_2Cl_2 (6 ×). To the resulting resin was added CH_2Cl_2 (2 mL) and trifluoroacetic acid (0.25 mL). The suspension was shaken for 1 hour, then rinsed with a CH_2Cl_2/trifluoroacetic acid (1:1) solution (2 ×) and CH_2Cl_2 (2 ×). The combined filtrates were concentrated and dried under high vacuum, affording the product **20** or **21** as the trifluoroacetic acid salt.

3-aminomethyl-3'-benzoylaminobiphenyl trifluoroacetic acid salt (20a)

Yellow oil (99% yield by ^1H NMR with tetrahydrofuran internal standard): ^1H NMR (300 MHz, CD_3OD) δ 8.16-8.12 (m, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.78-7.70 (m, 2H), 7.63-7.42 (m, 8H), 4.20 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.0, 143.3, 142.3, 140.5, 136.2, 135.1, 133.0, 130.8, 130.5, 129.7, 128.9, 128.9, 128.7, 128.6, 124.2, 121.6, 121.0, 44.4; FTIR (microscope) 3500-2400, 3282, 2920, 1604, 1126 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{20}H_{18}N_2O$ 302.14191, found 302.14219.

3-aminomethyl-3'-(4-chlorobenzoylamino)biphenyl trifluoroacetic acid salt (20b)

Yellow oil (100% yield by ^1H NMR with tetrahydrofuran internal standard): ^1H NMR (300 MHz, CD_3OD) δ 8.14-8.11 (m, 1H), 7.95 (d, J = 8.7 Hz, 2H), 7.78-7.69 (m, 2H), 7.62-7.42 (m, 7H), 4.20 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 167.8, 143.2, 142.3, 140.4, 139.1, 135.1, 134.8, 130.8, 130.5, 130.4, 129.9, 129.0, 128.9, 128.7, 124.3, 121.5, 121.0, 44.4; FTIR (microscope) 3500-2400, 3267, 3060, 2926, 1666, 1201 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{20}H_{17}N_2OCl$ 336.10294, found 336.10340.

3-aminomethyl-3'-(4-methoxybenzoylamino)biphenyl trifluoroacetic acid salt (20c)

Yellow oil (90% yield by ^{1}H NMR with tetrahydrofuran internal standard): ^{1}H NMR (300 MHz, CD_3OD) δ 8.14-8.10 (m, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.78-7.69 (m, 2H), 7.60-7.42 (m, 5H), 7.04 (d, J = 9.1 Hz, 2H), 4.20 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.3, 143.3, 142.2, 140.7, 139.5, 135.1, 130.8, 130.6, 130.4, 128.9, 128.9, 128.7, 128.1, 124.0, 121.6, 121.6, 121.1, 114.9, 56.0, 44.4; FTIR (microscope) 3500-2300, 3332, 3065, 2932, 1674, 1143 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{21}H_{20}N_2O_2$ 332.15247, found 332.15225.

4-amino-3'-benzoylaminobiphenyl trifluoroacetic acid salt (21a)

Yellow oil (98% yield by ^{1}H NMR with tetrahydrofuran internal standard): ^{1}H NMR (300 MHz, CD_3OD) δ 8.08-8.04 (m, 1H), 7.98-7.93 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.67-7.39 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.0, 142.4, 140.4, 139.8, 137.7, 136.3,, 132.9, 130.3, 129.6, 129.3, 128.6, 123.8, 120.9, 120.7, 120.5; FTIR (microscope) 3400-2600, 3308, 3058, 2924, 1604, 1483, 1199 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{19}H_{16}N_2O$ 288.12625, found 288.12622.

4-amino-3'-(4-chlorobenzoylamino)biphenyl trifluoroacetic acid salt (21b)

Yellow oil (75% yield by ^{1}H NMR with tetrahydrofuran internal standard): ^{1}H NMR (300 MHz, CD_3OD) δ 8.07-8.04 (m, 1H), 7.95 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.66-7.61 (m, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.49-7.41 (m, 2H), 7.37 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.7, 142.4, 140.3, 139.7, 139.0, 137.7, 134.9, 130.3, 129.8, 129.3, 128.2, 123.9, 120.9, 120.8, 120.5; FTIR (microscope) 3500-2400,

3285, 3060, 2925, 1673, 1202 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{19}H_{15}N_2OCl$ 322.08728, found 322.08748.

4-amino-3'-(4-methoxybenzoylamino)biphenyl trifluoroacetic acid salt (21c)

Yellow oil (89% yield by ^1H NMR with tetrahydrofuran internal standard): ^1H NMR (300 MHz, CD_3OD) δ 8.07-8.03 (m, 1H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.65-7.60 (m, 1H), 7.48-7.40 (m, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 164.3, 142.2, 140.6, 139.1, 139.0, 138.4, 130.6, 130.3, 129.3, 128.2, 123.7, 121.1, 121.0, 120.6, 114.9, 56.0; FTIR (microscope) 3700-2200, 3305, 3054, 2930, 1606, 1252 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{20}H_{18}N_2O_2$ 318.13684, found 318.13661.

4.9 References

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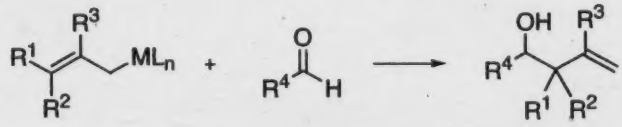
Chapter 5

Scandium-Catalyzed Enantioselective Addition of Chiral Allylboronates to Aldehydes

5.1 Introduction

Carbonyl allylation chemistry is one of the most useful tools in modern organic synthesis, particularly for the construction of polyacetate and polypropionate natural products.[1] Yet, despite extensive investigations, there is no general enantioselective method using simple and *stable* allylation reagents for the stereocontrolled formation of a wide variety of homoallylic alcohols (Equation 5-1).



Equation 5-1

Whereas many highly enantioselective allylation methods (Equation 5-1, R^1, R^2, R^3 = H) have been developed,[2] few of these procedures have been successfully extended to the enantioselective methallylation (Equation 5-1, R^1, R^2 = H, R^3 = Me) and crotylation (Equation 5-1, R^3 = H, R^1, R^2 = H, Me or Me, H) of aldehydes.

In fact, the crotylation of aldehydes with stable reagents to afford either *syn* or *anti* products predictably in a highly enantioselective manner (>95% ee) remains problematic. Indeed, while most crotylation methods using silicon or tin reagents give rise to *syn* products preferentially,[a] methods using chromium, titanium, zirconium, or indium generally provide *anti* products predominantly.[1a,2] Chiral crotylboron reagents have attracted particular attention in this area, as they can give access to both *syn* and *anti* products in a predictable fashion and in very high diastereoselectivity. A closed chair-like transition state has been postulated to account for the diastereospecificity of these reactions.[3] Examples of chiral crotylboration reagents include Brown's pinene-based **1**,[4] Roush's tartrate-derived **2**,[5] Masamune's borane **3**,[6] and Hoffmann's camphor-derived reagents **4**[7] (Figure 1). Despite their usefulness, methods using these reagents suffer from one or many drawbacks such as air and moisture sensitivity, low enantioselectivities, lengthy preparation of reagents, and poor reactivity.

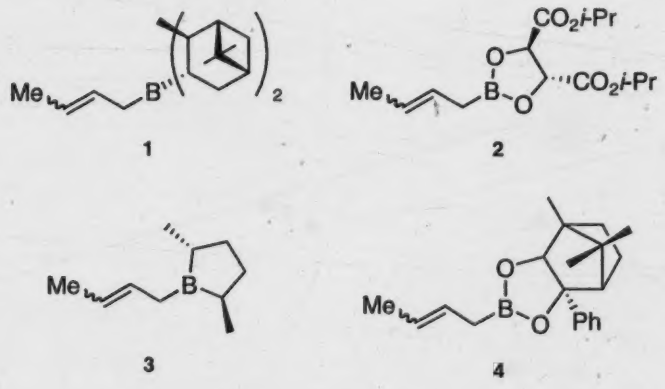


Figure 5-1. Common crotylboration reagents

[a] For a notable exception using silicon reagents, see ref 2i.

More recently, crotyltrichlorosilane reagents have also been shown to react diastereospecifically, presumably through a cyclic transition state. Despite their high efficiency with aromatic aldehydes, crotylsilylation methods based on chiral phosphoramide[8] or *N*-oxide[9] catalysts are incompatible with aliphatic aldehydes.

Given the importance of the products of allylation, methallylation, and crotylation reactions, we set out to develop the first general, highly enantio- and diastereoselective system for the allylation of aldehydes based on a conveniently handled, stable boron-based reagent.[10]

5.2 Optimization

Following the discovery of Lewis acid-catalyzed allylborations by our group[11] and others,[12] we reported on the use of chiral allylboronates in highly diastereo- and enantioselective allylation, methallylation, and crotylation reactions.[13] This new approach to the allylation of aldehydes uses Hoffmann's air-stable allylboronates under $Sc(OTf)_3$ catalysis. Interestingly, Hoffmann's boronates were developed over twenty years ago and were the first chiral allylboron reagents ever reported.[2g] Significant advantages of these boronates are their stability and the availability of camphor in both enantiomeric forms. Our new Lewis acid-catalyzed procedure provides the benefit of increased reactivity at low temperatures, which significantly improves substrate scope and stereoselectivity. Indeed, a wide variety of aldehydes can be employed successfully, including functionalized aliphatic aldehydes that are useful for the elaboration of complex

natural products. Herein, we present the optimization of this methodology, its scope and the demonstration of its gram-scale capability.

In the development of stable boron-based allylation reagents, boronates are preferred because of their superior stability over boranes. When we started this work, however, there were no chiral allylboronic esters known to afford practical levels of enantioselectivity (>95% ee) in additions to achiral aldehydes under typical low-temperature conditions (-78 °C).[1a,2] On the basis of the potential beneficial effect of a lower reaction temperature and the different mechanistic nature of the Lewis acid-catalyzed manifold on the enantioselectivity, we revisited a number of known chiral diol auxiliaries for boronic acids. In our initial series of experiments, Hugo Lachance and I investigated the allylation of benzaldehyde using various solvents, temperatures, and acids identified from our previous studies.[11] A small set of allylboronates **5** derived from chiral diol precursors **a-e** was compared under a number of different conditions (Figure 5-2).

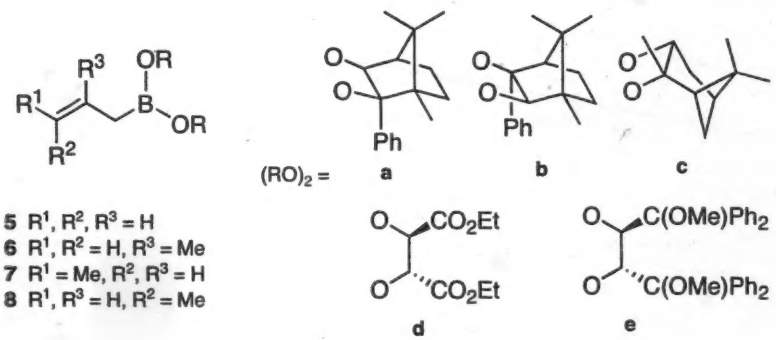


Figure 5-2. Chiral allylboronates

Using allylboronate (–)-**5a**, these investigations revealed that $Sc(OTf)_3$ provides the best combination of rate and enantioselectivity in the formation of homoallylic alcohol **9** (Table 5-1, entries 1-7). A pronounced solvent effect was also observed, with dichloromethane standing out as the most efficient one both in terms of conversion and ee (entries 7-12). Whereas pinanediol-based **5c** and the tartrate-based reagents **5d**[2d] and **5e**[14] gave low enantioselectivity (entries 14-16), the Hoffmann camphor-derived allylboronates **5a** and **5b**[2g] gave excellent results (entries 7, 13). Further optimization confirmed that the preferred order of addition involves mixing $Sc(OTf)_3$ in CH_2Cl_2 at -78 °C, followed by the aldehyde and a solution of the allylboronate in CH_2Cl_2.

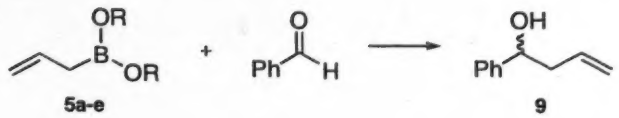


Table 5-1. Lewis acid-catalyzed allylboration of benzaldehyde[a]

entry	boronate	acid	solvent	temp. (°C)	conv.[b] (%)	ee[c] (%)
1[d]	**5a**	none	CH_2Cl_2	25	50	11
2	**5a**	$AlCl_3$	CH_2Cl_2	-78	14	63
3	**5a**	$TiCl_4$	CH_2Cl_2	-78	22	78
4	**5a**	TfOH	CH_2Cl_2	-78	72	84
5	**5a**	$Cu(OTf)_2$	CH_2Cl_2	-40	4	52
6	**5a**	$Yb(OTf)_3$	CH_2Cl_2	-40	4	38
7	**5a**	$Sc(OTf)_3$	CH_2Cl_2	-78	90	92
8[e]	**5a**	$Sc(OTf)_3$	CH_2Cl_2	-78	72	93
9	**5a**	$Sc(OTf)_3$	toluene	-78	30	46
10	**5a**	$Sc(OTf)_3$	hexanes	-78	20	8
11	**5a**	$Sc(OTf)_3$	Et_2O	-78	4	-
12	**5a**	$Sc(OTf)_3$	THF	-78	0	-
13	**5b**	$Sc(OTf)_3$	CH_2Cl_2	-78	62	84[f]
14	**5c**	$Sc(OTf)_3$	CH_2Cl_2	-78	100	9
15	**5d**	$Sc(OTf)_3$	CH_2Cl_2	-78	100	7
16	**5e**	$Sc(OTf)_3$	CH_2Cl_2	0	0	-

[a] Typical reaction conditions: 0.44 mmol of (–)-**5**, 0.40 mmol of benzaldehyde, 0.04 mmol of Lewis acid, 1 mL of solvent, -78 °C, 2 hours reaction time. [b] Measured by integration of benzyl alcohol vs. benzaldehyde ^{1}H NMR signals after work-up (see section 5.4). [c] Measured by chiral HPLC (see section 5.7). [d] 72 hours reaction time. [e] 4 Å molecular sieves (10 mg) were added. [f] The opposite enantiomer is predominant.

An important feature of Hoffmann's allylboronates is their relative stability. Indeed, they can be purified by chromatography and handled without any special precautions. Moreover, the diol precursor of allylboronate **5a** can be easily synthesized

without chromatographic purification in four steps from camphorquinone,[2g] which is commercially available in both enantiomeric forms. While the enantioselectivities and the rates originally reported were modest (see entry 1, with no catalyst),[2g] the results obtained under our new catalytic manifold are remarkable.

5.3 Substrate scope

In order to study the scope of our methodology, various aldehydes were reacted with boronates **5a**-**8a**. Allylation and methallylation reactions using **5a** and **6a** were performed by Hugo Lachance, while crotylations using **7a** and **8a** were performed by Xiaosong Lu and myself, respectively. As shown in Table 5-2, allylations of aromatic, aliphatic, and propargylic aldehydes using boronates **5a**-**8a** generally proceeded in good yields and with very high ee's.

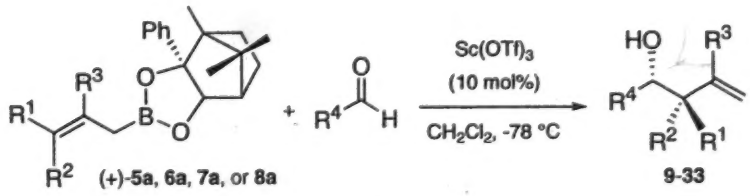


Table 5-2. Substrate scope for the $Sc(OTf)_3$-catalyzed addition of allylboronates **5a**-**8a** to aldehydes.[a]

entry	boronate (R^1, R^2, R^3)	aldehyde (R^4)	product[b]	yield[c] (%)	ee[d] (%)
1	**5a** (H, H, H)	Ph	**9**	85	92
2	**5a**	$PhCH_2CH_2$	**10**	64	97
3	**5a**	$TBDPSO(CH_2)_2$	**11**	86	93

4	**5a**	$BnOCH_2$	**12**	62	77
5	**5a**	$TBDMSOCH_2$	**13**	76	90
6	**5a**	$TBDPSOCH_2$	**14**	61	90
7	**5a**	$H_{11}C_5CC$	**15**	87	95
8[e]	**5a**	C_6H_{11}	**16**	53	92
9	**6a** (H, H, Me)	Ph	**17**	64	98
10	**6a**	$PhCH_2CH_2$	**18**	76	97
11	**6a**	$TBDPSO(CH_2)_2$	**19**	77	97
12	**6a**	$BnOCH_2$	**20**	70	97
13	**6a**	$TBDMSOCH_2$	**21**	88	95
14[e]	**6a**	$H_{11}C_5CC$	**22**	95	97
15	**6a**	C_6H_{11}	**23**	63	92
16	**7a** (Me, H, H)	Ph	**24**	60	97
17	**7a**	$PhCH_2CH_2$	**25**	71	96
18	**7a**	$TBDPSO(CH_2)_2$	**26**	63	94
19	**7a**	$TBDMSOCH_2$	**27**	63	96
20	**7a**	$H_{11}C_5CC$	**28**	78	97
21	**8a** (H, Me, H)	Ph	**29**	53	59
22	**8a**	$PhCH_2CH_2$	**30**	52	96
23	**8a**	$TBDPSO(CH_2)_2$	**31**	57	96
24	**8a**	$TBDMSOCH_2$	**32**	57	98
25	**8a**	$H_{11}C_5CC$	**33**	61	95
26[f]	**8a**	$PhCH_2CH_2$	**30**	65	90
27[g]	**8a**	$PhCH_2CH_2$	**30**	48	-[i]
28[h]	**8a**	$PhCH_2CH_2$	**30**	<10	-[i]

[a] Typical reaction conditions: 0.4 mmol of aldehyde in CH_2Cl_2 (0.5 M) with 10 mol % $Sc(OTf)_3$ at -78 °C followed by addition of allylboronate (entries 1-15: 1.1 equiv., entries 16-20: 1.5 equiv.). Entries 21-28 are with 1.5 equiv. of aldehyde. Reaction time: 12-24 h. [b] The diastereomeric ratio for entries 16-28 was always over 50:1 (determined by ^1H NMR). [c] Yields of pure products isolated after flash chromatography. [d] Measured by chiral HPLC on the free alcohol or a derivative thereof, or through NMR analysis of Mosher esters (see section 5.7). The absolute configuration was determined by comparison of optical rotation with known compounds. [e] Reaction performed on a 6 mmol scale. [f] Trifluoroacetic acid (10 mol %) was used instead of $Sc(OTf)_3$. [g] $TiCl_4$ (10 mol %) was used instead of $Sc(OTf)_3$. [h] $AlCl_3$ (10 mol %) was used instead of $Sc(OTf)_3$. [i] Not measured.

The simple allylation using **5a** (entries 1-8) smoothly provides homoallylic alcohols **9-16** and is usually complete within 4 hours, with the exception of α-branched aldehydes (entry 8). Although the lower ee obtained with benzyl-protected hydroxyacetaldehyde is disappointing (entry 4), its TBDMS-protected equivalent provides satisfactory results (entry 5). Methallylation using **6a** also constitutes a very efficient process (entries 9-15), providing products **17-23**. Interestingly, this method represents one of the most efficient enantioselective procedure for the methallylation of aldehydes to date, combining both substrate generality and high enantioselectivities.[1a,2] Most significantly, the (*E*)- and (*Z*)-crotylboronates **7a** and **8a** provide the respective *anti* and *syn* products **24-33** in good yields and high enantioselectivity (entries 16-25). Moreover, the diastereoselectivity observed in reactions using crotylboronates **7a** and **8a** is consistently very high (>95% de). Interestingly, the ee obtained for the crotylation of benzaldehyde using **8a** is much lower than any other observed in this study (entry 21). We believe that the increased steric bulk of benzaldehyde may distort the chair-like transition state in order to alleviate a *syn*-pentane interaction, leading to reduced selectivity (Figure 5-3).

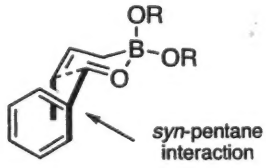


Figure 5-3. Transition state structure for the *Z*-crotylboration of benzaldehyde

Although crotylborations using **7a** and **8a** are slower than allylations using **5a** or methallylations using **6a**, good yields can be obtained by simply using a small excess of either the boronate or the aldehyde. Other attempts to improve the yields of crotylborations by using different acids (entries 26-28), or by increasing the catalyst loading, the concentration, or the reaction times have, thus far, not led to improvements. We are presently exploring the use of more Lewis acidic Sc(III) sources to increase the rate of these crotylboration reactions.

Since our first report, we have found that α-branched aldehydes can undergo allylation with **5a** and **6a**, albeit at a slower rate (entries 8, 15). Additionally, we have discovered that propargylic aldehydes are very suitable substrates for allylations using **5a**-**8a**. The application of our methodology to this class of substrates represents a complementary approach to the enantioselective addition of terminal alkynes to aldehydes, for which unstable β,γ-unsaturated aldehydes would be required.[15] Of particular significance is the use of crotylboration reagents **7a** and **8a** in this process. To the best of our knowledge, no other method has been reported for the direct and highly enantioselective crotylation of propargylic aldehydes.[16,17,18] Interestingly, we noticed that the scandium catalyst exhibits very poor solubility in these reactions, suggesting the possibility of using a reduced catalyst loading, especially for reactions on a larger scale (*vide infra*). The absolute configuration of alcohols **24**, **25**, **26**, **29** and **31** was assigned by comparison of the sign of their optical rotation to that of known samples. The absolute configuration of all the other products was assigned by analogy.

In our original procedure, a DIBAL-H quench of the reaction mixture was followed by the addition of dilute acid. This standard workup procedure is required to eliminate any unreacted aldehyde, and to hydrolyze the borate product initially formed in the reaction. Unfortunately, this procedure allowed the recovery of only small amounts of the diol auxiliary (20-30%). We have since found that a simple basic workup following the DIBAL-H quench leads to a much improved recovery of the diol auxiliary. In a typical experiment, the reaction mixture is quenched by the addition of 2 equivalents of DIBAL-H and stirred at -78 °C for 1 hour. A 1 M aqueous solution of NaOH is then carefully added and a liquid-liquid extraction provides a crude mixture containing both the homoallylic alcohol and the diol auxiliary. In this way, the diol auxiliary is cleanly cleaved from the borate product and does not tend to decompose as is the case with our original acidic workup. Additionally, any unreacted allylboronate can easily be oxidized and hydrolyzed to maximize the recovery of the diol.[19] It is noteworthy that only one equivalent of diol auxiliary is generated from the reaction, simplifying the subsequent purification compared to other popular allylboron reagents.[2a]

5.4 Gram-scale applications

In order to test the practical potential of this system, we performed selected examples of allyl-, methallyl- and crotylborations on a gram-scale. As can be seen from Table 5-3, reagents **5a-8a** all give satisfactory results on a preparative scale. Importantly, the diol auxiliary can be recovered in good yield in all cases for which the new basic

workup was performed (entries 1-2 and 4-6). These results point to the potential application of this methodology in natural product synthesis.

Table 5-3. Gram-scale addition of allylboronates **5a-8a** to aldehydes.[a]

entry	boronate	product	yield (%)		ee[d]
			product[b]	diol[c]	(%)
1	**5a**	**11**	65	78	97
2	**5a**	**15**	60	80	98
3	**6a**	**19**	71	-[e]	96
4	**6a**	**22**	95	65	97
5	**7a**	**28**	75	75	96
6	**8a**	**33**	72	75	95

[a] See section 5.7 for reaction conditions. [b] Yields of pure homoallylic alcohol products isolated after flash chromatography. [c] Combined recovery yield of diol from the allylboration and the oxidation/hydrolysis of unreacted allylboronate. [d] Measured by NMR analysis of the Mosher ester derivatives. [e] The original acidic workup was used and no diol isolation was achieved.

5.5 Mechanistic considerations

On the basis of preliminary arguments presented earlier[11] and the fact that the crotylation reactions proceed diastereospecifically, these allylboration reactions are thought to proceed through the usual closed chair-like transition state. Although the exact nature of the Lewis acid catalysis remains speculative at the moment, we propose an activation of the boronate via coordination of the scandium to one of the two exocyclic oxygen atoms (Figure 5-4). This coordination should increase the electrophilicity of the boron atom, a factor that was shown to be determinant in the reactivity of allylboron

reagents.[20] The factors that determine the facial selectivity remain unclear, although an attractive interaction between the aldehyde and the phenyl group has been proposed for related systems.[2g,21] Further studies are ongoing in our laboratories to determine the precise mechanism of these reactions.

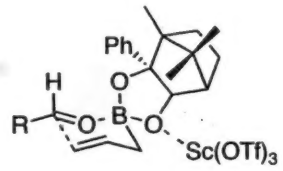


Figure 5-4. Proposed transition state structure for the Lewis acid-catalyzed addition of allylboronates

5.6 Conclusion

In conclusion, we have developed a remarkably general method for the enantioselective allylation, methallylation, and crotylation of aldehydes using Lewis acid catalysis. Of particular importance is the fact that this method uses stable, chiral allylboronates to give access to a wide range of homoallylic alcohols in very high diastereo- and enantioselectivity.

5.7 Experimental

5.7.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. All aldehydes were purified by bulb-to-bulb distillation prior to use. Boronates **5a**, **6a**, **7a**, and **8a** were used within 24 hours after their purification. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and were visualized with UV light and 5% phosphomolybdic acid/EtOH (PMA). NMR spectra were recorded on a Bruker AM 300, Bruker AM 200, Varian INOVA-300, INOVA-400 or INOVA-500 instrument. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts. Boron NMR spectra were referenced to external $BF_3{\cdot}OEt_2$; ^{19}F spectra were referenced to external $CFCl_3$. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 instrument. Optical rotations were recorded using Perkin-Elmer PE-241. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 system. The enantiomeric excess for compounds **13**, **15-16**, **19**, **21-23**, **28**, **33, and 35** was determined using integration of the ^{19}F NMR signals of the corresponding Mosher ester derivatives.[22] The enantiomeric excess for compounds **9-12**, **14**, **17-18**, **20**, **24-27**, **29-32** was determined using an HP 1100 HPLC system. The enantiomeric excess for compounds **27** and **32** was determined on the corresponding phenylisocyanate adduct using an HP 1100 HPLC system. Chiralcel AD-RH, Chiralcel OD-RH, Chiralcel OD,

and Chiralcel AD columns were purchased from Chiral Technologies Inc. Racemic homoallylic alcohols were prepared in the same manner using the pinacol boronate derivatives. The absolute stereochemistry for compounds **24**, **25**, **26**, **29**, and **31** was determined by comparison of the sign of optical rotation with reported literature values. The absolute stereochemistry for all other homoallylic alcohols was assigned by analogy. For Table 2, products **5a**, **6a**, and **9-23** were prepared by Hugo Lachance, products **7a** and **24-28** were prepared by Xiaosong Lu, and products **8a** and **29-33** were prepared by myself.

5.7.2 Preparation of allylboronates 7a-8a

(1*R*,2*S*,3*R*,4*S*)-2,3-O-[(*E*)-2-butenylboryl]-2-phenyl-1,7,7-trimethylbornanediol (7a)

A 200-mL three-neck round-bottom flask equipped with a magnetic stir bar and a thermometer was charged with THF (110 mL) and KOtBu (4.65 g, 41.5 mmol). This mixture was cooled to –78 °C, and *trans*-2-butene (2.46 g, 43.9 mmol) was added via cannula. *n*-BuLi (1.43 M in hexane, 29 mL, 41.5 mmol) was then added dropwise over 1 hour using a syringe pump, so that the internal temperature did not rise above –73 °C. After completion of the addition, the reaction mixture was allowed to warm until the internal temperature reached –50 °C. The solution was maintained at –50 °C for 15 minutes, then cooled back to –78 °C. Triisopropylborate (10.5 mL, 45.6 mmol) was then added dropwise over 30 minutes through a syringe pump. The resulting solution was maintained at –78 °C for 2 hours, then sealed with Ar and stored at –20 °C for a few weeks without any noticeable change of its quality. To this solution (10 mL, approx. 2.7 mmol) was added 1 N HCl (15 mL), and the resulting biphasic mixture was extracted

with Et_2O (3 × 25 mL). To the combined organic layers was added (1*R*,2*S*,3*R*,4*S*)-2-phenyl-1,7,7-trimethylbornanediol (**a**)[2g] (220 mg, 0.89 mmol) and $MgSO_4$ (approx. 500 mg). The resulting mixture was stirred at ambient temperature for 45 minutes, filtered. and concentrated under reduced pressure. Flash chromatography (5% EtOAc/hexanes, SiO_2 pre-treated with 5% Et_3N/hexanes) yielded a colourless oil (277 mg, 99%).

^1H NMR (500 MHz, $CDCl_3$): δ 7.42-7.41 (m, 2H), 7.34-7.24 (m, 3H), 5.43-5.30 (m, 2H), 4.71 (s, 1H), 2.13 (d, J = 5.5 Hz, 1H), 1.84-1.78 (m, 1H), 1.61-1.52 (m, 5H), 1.20-1.13 (m, 5H), 1.04-0.94 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H).

(1*R*,2*S*,3*R*,4*S*)-2,3-O-[(*Z*)-2-butenylboryl]-2-phenyl-1,7,7-trimethylbornanediol (8a)

A 300-mL three-neck round-bottom flask equipped with a magnetic stir bar and a thermometer was charged with THF (110 mL) and KOtBu (2.86 g, 25.5 mmol). This mixture was cooled to –78 °C, and *cis*-2-butene (1.50 g, 26.8 mmol) was added via cannula. *n*-BuLi (1.43 M in hexane, 17.9 mL, 25.5 mmol) was then added dropwise over 1 hour, such that the internal temperature did not rise above –70 °C. After completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm up until the internal temperature reached –50 °C. The solution was maintained at that temperature for 30 minutes, then cooled to –78 °C. Triisopropylborate (6.48 mL, 28.1 mmol) was added dropwise over 30 minutes. The reaction mixture was maintained at –78 °C for 2 hours, then rapidly poured into a 500-mL separatory funnel containing 1 N HCl (200 mL). The layers were separated, then the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered before being concentrated *in vacuo* to a volume of 63 mL. The resulting solution was

approximately 0.4 M in (*Z*)-2-butenylboronic acid, and could be kept at 4 °C for a few weeks without any noticeable change in its concentration or its reactivity with diols. To this solution (3.00 mL, 1.20 mmol) was added (1*R*,2*S*,3*R*,4*S*)-2-phenyl-1,7,7-trimethylbornane-diol (**a**)[2g] (246 mg, 1.00 mmol) and $MgSO_4$ (approx. 500 mg). The resulting mixture was stirred at ambient temperature for 30 minutes, filtered, and concentrated under reduced pressure. Flash chromatography (10% EtOAc/hexanes, SiO_2 pre-treated with 5% Et_3N/hexanes) yielded a colourless oil (307 mg, 99%): TLC (15% EtOAc/hexanes, PMA): 0.58; $[\alpha]^{25}_D$ +12.8° (*c* = 1.73, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.38 (m, 2H), 7.35-7.22 (m, 3H), 5.52-5.34 (m, 2H), 4.70 (s, 1H), 2.13 (d, *J* = 5.2 Hz, 1H), 1.87-1.74 (m, 1H), 1.66-1.61 (m, 2H), 1.54-1.50 (m, 3H), 1.21 (s, 3H), 1.21-1.10 (m, 2H), 1.07-0.96 (m, 1H), 0.94 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 127.4, 127.2, 126.7. 124.9, 123.5, 95.7, 88.6, 52.0, 50.2, 48.9, 29.6, 24.7, 23.6, 20.7, 12.5, 9.3; ^{11}B NMR (128 MHz, $CDCl_3$): δ 34.1; FTIR (CH_2Cl_2 cast, cm^{-1}): 3020, 2957, 1446, 1340, 1035; HRMS (EI, *m/z*) Calcd for $C_{20}H_{27}O_2B$: 310.21042. Found: 310.21036; Anal. Calcd for $C_{20}H_{27}O_2B$: C, 77.43; H, 8.77. Found: C, 77.41; H, 8.77.

5.7.3 Synthesis of *anti*-homoallylic alcohols 24-28

General procedure

Scandium trifluoromethanesulfonate (16 mg, 0.03 mmol) and CH_2Cl_2 (0.3 mL) were introduced in a 10-mL round-bottom flask, and the mixture was cooled to –78 °C. The aldehyde (0.45 mmol) was added, followed by a solution of boronate **7a** (93 mg, 0.30 mmol) in CH_2Cl_2 (0.3 mL) dropwise over 5 minutes. The resulting mixture was stirred at

–78 °C for 24 hours, then DIBAL-H (1.0 M in toluene, 0.67 mL, 0.67 mmol) was added. The mixture was stirred at –78 °C for 30 minutes, then 1 N HCl (5 mL) was carefully added and the flask was allowed to warm up to ambient temperature. The resulting layers were separated, then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded the pure homoallylic alcohol.

(1*R*,2*R*)-2-Methyl-1-phenyl-3-buten-1-ol (24)[23]

Colourless oil (29 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H), 5.80 (ddd, J = 17.2, 10.5, 8.2 Hz, 1H), 5.20-5.15 (m, 2H), 4.35 (d, J = 7.8 Hz, 1H), 2.49-2.45 (m, 1H), 2.15 (br s, 1H), 0.86 (d, J = 6.8 Hz, 3H).

(3*S*,4*R*)-4-Methyl-1-phenyl-5-hexen-3-ol (25)[5]

Colourless oil (41 mg, 71%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.15 (m, 5H), 5.73 (ddd, J = 16.7, 10.8, 8.2 Hz, 1H), 5.12-5.08 (m, 2H), 3.40 (ddd, J = 9.1, 6.0, 3.1 Hz, 1H), 2.85-2.63 (m, 2H), 2.23-2.19 (m, 1H), 1.86-1.65 (m, 2H), 1.56 (br s, 1H), 1.02 (d, 3H, J = 6.9 Hz).

(3*S*,4*R*)-1-(*t*-Butyldiphenylsilyloxy)-4-methyl-5-hexen-3-ol (26)[24]

Colourless oil (70 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72-7.67 (m, 4H), 7.44-7.35 (m, 6H), 5.90 (ddd, J = 16.7, 11.1, 8.0 Hz, 1H), 5.08-5.04 (m, 2H), 3.90-3.82, (m, 2H), 3,77-3.74 (m, 1H), 2.97 (br s, 1H), 2.27-2.23 (m, 1H), 1.71-1.63 (m, 2H), 1.06 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H).

(2*R*,3*R*)-1-(*t*-Butyldimethylsilyloxy)-3-methyl-4-penten-2-ol (27)

Colourless oil (44 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (m, 1H), 5.06-5.02 (m, 2H), 3.63-3.60 (m, 1H), 3.50-3.47 (m, 2H), 2.35 (d, J = 2 Hz, 1H), 2.30 (apparent sextet, J = 7.0 Hz, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

(3*R*,4*R*)-3-Methyl-1-undecen-5-yn-4-ol (28)

Colourless oil (48 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (ddd, J = 17.7, 10.4, 7.6 Hz, 1H), 5.17-5.12 (m, 2H), 4.19 (ddd, J = 6.2, 3.8, 1.9 Hz, 1H), 2.44-2.40 (m, 1H), 2.21 (ddd, J = 9.0, 7.1, 1.9 Hz, 2H), 1.82 (br s, 1H), 1.54-1.48 (m, 2H), 1.40-1.29 (m, 4H), 1.12 (d, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H).

5.7.4 Synthesis of *syn*-homoallylic alcohols 29-33

General procedure

Scandium trifluoromethanesulfonate (16 mg, 0.03 mmol) and CH_2Cl_2 (0.3 mL) were introduced in a 10-mL round-bottom flask, and the mixture was cooled to –78 °C. The aldehyde (0.50 mmol) was added, followed by a solution of boronate **8a** (102 mg, 0.33 mmol) in CH_2Cl_2 (0.3 mL) dropwise over 5 minutes. The resulting mixture was stirred at –78 °C for 24 hours, then DIBAL-H (1.0 M in toluene, 1.00 mL, 1.00 mmol) was added. The mixture was stirred at –78 °C for 30 minutes, then 1 N HCl (5 mL) was carefully added and the flask was allowed to warm up to ambient temperature. The resulting layers were separated, then the aqueous layer was extracted with EtOAc (3 × 5

mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded the pure homoallylic alcohol.

(1*R*,2*S*)-2-Methyl-1-phenyl-3-buten-1-ol (29)[25]

Colourless oil (28.5 mg, 53%): TLC (10% EtOAc/toluene, PMA): 0.23; $[\alpha]^{25}_{D}$ +12.0° (*c* = 1.47, $CHCl_3$, lit.:[5,25] –15.0° for the opposite enantiomer, +15.2°); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H), 5.83-5.70 (m, 1H), 5.10-5.07 (m, 1H), 5.05-5.02 (m, 1H), 4.63 (d, *J* = 5.5 Hz, 1H), 2.66-2.53 (m, 1H), 1.91 (br s, 1H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 140.3, 128.0, 127.3, 126.5, 115.5, 77.3, 44.6, 14.0; HPLC: Chiralcel OD-RH, 35% *i*PrOH/H_2O, 0.40 mL/min., UV detection at 210 nm, major peak at 61.5 min., minor peak at 68.7 min., 59% ee.

(3*S*,4*S*)-4-Methyl-1-phenyl-5-hexen-3-ol (30)[26]

Colourless oil (32 mg, 52%): TLC (10% EtOAc/toluene, PMA): 0.35; $[\alpha]^{25}_{D}$ –32.5° (*c* = 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.20-7.14 (m, 3H), 5.79-5.72 (m, 1H), 5.10-5.07 (m, 1H), 5.06-5.05 (m, 1H), 3.50 (ddd, *J* = 8.8, 5.0, 3.1 Hz, 1H), 2.84 (ddd, *J* = 13.9, 10.2, 5.3 Hz, 1H), 2.63 (ddd, *J* = 13.7, 9.8, 6.7 Hz, 1H), 2.32-2.24 (m, 1H), 1.84-1.77 (m, 1H), 1.72-1.63 (m, 1H), 1.41 (br s, 1H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 140.7, 128.4, 128.4, 125.8, 115.5, 74.1, 43.6, 35.8, 32.4, 14.2; HPLC: Chiralcel AD-RH, 40% *i*PrOH/H_2O, 0.33 mL/min., UV detection at 210 nm, major peak at 53.9 min., minor peak at 60.0 min., 96% ee.

(3*S*,4*S*)-1-(*t*-Butyldiphenylsilyloxy)-4-methyl-5-hexen-3-ol (31)[27,28]

Colourless oil (69.5 mg, 57%): TLC (5% EtOAc/toluene, PMA): 0.29; $[\alpha]^{25}_{D}$ –4.4° (*c* = 1.89, $CHCl_3$, lit.:[27,28] +3.3°, +5.5° for the opposite enantiomer); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.44-7.36 (m, 6H), 5.77 (ddd, 1H, *J* = 17.4, 10.4, 7.6 Hz), 5.60-5.00 (m, 2H), 3.90-3.80 (m, 2H), 3.74 (ddd, 1H, *J* = 8.8, 6.0, 2.6 Hz), 3.12 (br s, 1H), 2.32-2.24 (m, 1H), 1.74-1.60 (m, 2H), 1.11 (d, 3H, *J* = 6.9 Hz), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 135.6, 135.5, 135.5, 133.1, 133.0, 129.8, 129.8, 127.7, 114.8, 74.8, 63.6, 43.9, 35.5, 26.8, 19.0, 15.1; HPLC: Chiralcel AD-RH, 55% *i*PrOH/H_2O, 0.30 mL/min., UV detection at 210 nm, minor peak at 24.6 min., major peak at 28.2 min., 96% ee.

(2*R*,3*S*)-1-(*t*-Butyldimethylsilyloxy)-3-methyl-4-penten-2-ol (32)

Colourless oil (43 mg, 57%): TLC (5% EtOAc/toluene, PMA): 0.20; $[\alpha]^{25}_{D}$ –15.9° (*c* = 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70 (ddd, 1H, *J* = 18.3, 10.3, 8.0 Hz), 5.06-4.97 (m, 2H), 3.66-3.60 (m, 1H), 3.48-3.39 (m, 2H), 2.44 (d, 1H, *J* = 3.7 Hz), 2.26 (apparent sextet, 1H, *J* = 7.0 Hz), 1.07 (d, 3H, *J* = 6.8 Hz), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 114.9, 74.7, 65.2, 41.0, 25.8, 18.2, 16.0, -5.4; FTIR (CH_2Cl_2 cast, cm^{-1}): 3574, 3482, 3078, 2956, 2929, 2857, 1640, 1463, 1257, 1100, 837; HRMS (EI, *m*/*z*) Calcd for $C_{12}H_{26}O_2NaSi$: 253.15943. Found: 253.15936; HPLC (performed on the carbamate derivative from reaction with phenylisocyanate): Chiralcel OD, 2% *i*PrOH/hexane, 0.30 mL/min., UV detection at 210 nm, major peak at 20.8 min., minor peak at 23.3 min., 98% ee.

(3*S*,4*R*)-3-Methyl-1-undecen-5-yn-4-ol (33)

Colourless oil (36 mg, 61%): TLC (15% EtOAc/hexanes, PMA): 0.34; $[\alpha]^{25}_{D}$ +22.7° (*c* = 1.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94-5.80 (m, 1H), 5.20-5.17 (m, 1H), 5.15-5.12 (m, 1H), 4.26 (ddd, 1H, *J* = 4.8, 2.0, 2.0 Hz), 2.50-2.38 (m, 1H), 2.22 (ddd, 2H, *J* = 6.9, 6.9, 2.0 Hz), 1.72 (br s, 1H), 1.57-1.46 (m, 2H), 1.44-1.26 (m, 4H), 1.11 (d, 3H, *J* = 6.9 Hz), 0.91 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 116.8, 86.7, 79.2, 66.3, 44.5, 31.0, 28.4, 22.1, 18.6, 15.6, 13.9; FTIR (neat, cm^{-1}): 3389, 3080, 2933, 1459, 1020; HRMS (EI, *m*/*z*) Calcd for $C_{12}H_{20}O$: 180.15141. Found: 180.15092; ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.90 (major), -72.19 (minor) 95% ee on the Mosher ester derivative.

5.7.5 Gram-scale synthesis of homoallylic alcohols

Typical procedure: (3*S*,4*R*)-3-Methyl-1-undecen-5-yn-4-ol (33)

Scandium trifluoromethanesulfonate (238 mg, 0.48 mmol) and CH_2Cl_2 (5 mL) were introduced in a 50-mL round-bottom flask, and the mixture was cooled to –78 °C. 2-Octynal (1.03 mL, 7.25 mmol) was added, followed by a solution of boronate **8a** (1.50 g, 4.83 mmol) in CH_2Cl_2 (7 mL) dropwise over 30 minutes. The resulting mixture was stirred at –78 °C for 24 hours, then DIBAL-H (1.0 M in toluene, 14.5 mL, 14.5 mmol) was added. The mixture was stirred at –78 °C for 1 hour, then carefully poured into a 250-mL separatory funnel containing 1 N NaOH (50 mL). The resulting layers were separated, then the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded homoallylic alcohol **33** as a colourless oil (570 mg, 72%).

The fractions containing the diol auxiliary and the ones containing diol-boronate derivatives were concentrated, then treated with a solution of THF (2 mL), 1 N NaOH (1 mL), and H_2O_2 (1 mL of a 30% aqueous solution) for 16 hours. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded (1*R*,2*S*,3*R*,4*S*)-2-phenyl-1,7,7-trimethylbornanediol (**a**) (891 mg, 75%).

5.8 References

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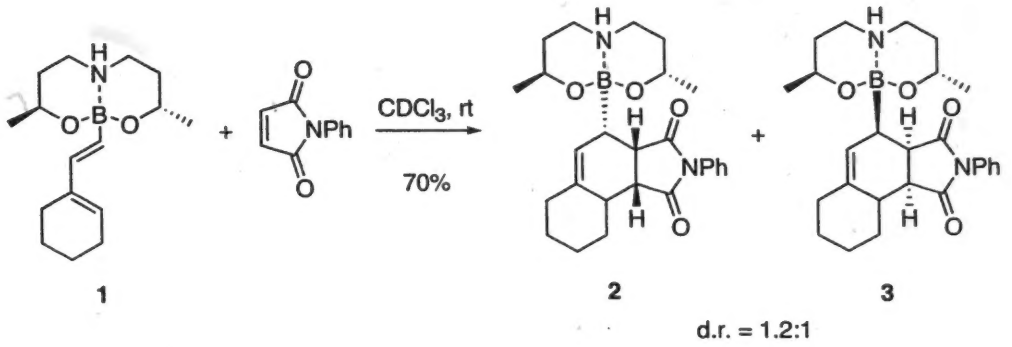
Chapter 6

Reactions of alkenylboronic acid-diethanolamine adducts

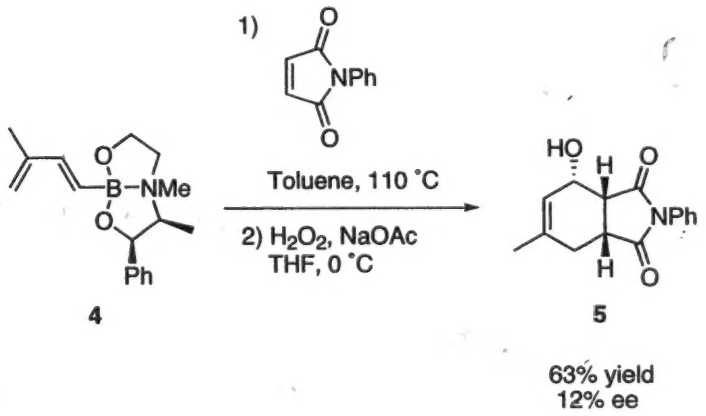
6.1 Introduction

The Diels-Alder reaction is of tremendous importance for the construction of six-membered carbocycles and, accordingly, the development of asymmetric versions of this reaction has attracted a lot of attention.[1] To date, most asymmetric versions of the Diels-Alder reaction have utilized chiral Lewis acids both as activators, and as the source of chirality for the reaction.[1a] Although extremely useful, this approach suffers from the limited number of suitable substrates for which the reaction provides high yields and selectivities. The opposite strategy, the use of a Lewis base as the promoter for an asymmetric Diels-Alder reaction, was first reported by Wang.[2] This approach involved using a dienylboronic acid-diethanolamine adduct (**1**) as the diene and *N*-phenylmaleimide as the dienophile (Scheme 6-1). Formation of the diethanolamine adduct **1** significantly enhanced the intrinsically poor reactivity of the dienylboronic acid. In the Diels-Alder reaction, a modest level of stereoinduction was observed as a consequence of the chirality of the diethanolamine derivative. Additionally, the cycloaddition yielded the *endo* adducts **2** and **3** exclusively.



Scheme 6-1

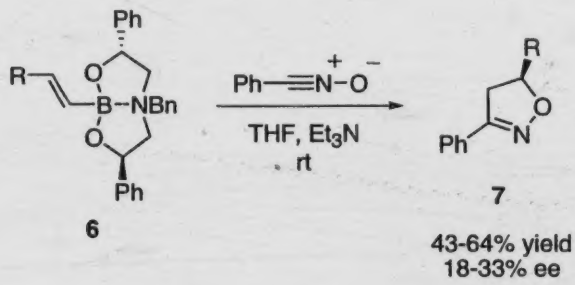
In a related study, Mortier and co-workers reacted the ephedrine-derived dienyl boronate **4** with *N*-phenylmaleimide (Scheme 6-2).[3] Following a basic oxidative workup, the *endo* cycloadduct **5** was obtained in a poor 12% enantiomeric excess.



Scheme 6-2

In another type of reaction involving boronic acid-diethanolamine adducts, Marsden and co-workers reacted vinylboronate derivatives **6** with nitrile oxides in a [3+2]

dipolar cycloaddition (Scheme 6-3).[4] The resulting isoxazoline products **7** are useful synthetic intermediates and can give access to aldol-like products.[5] Again, the selectivities obtained in this study were too low to be of any synthetic value.



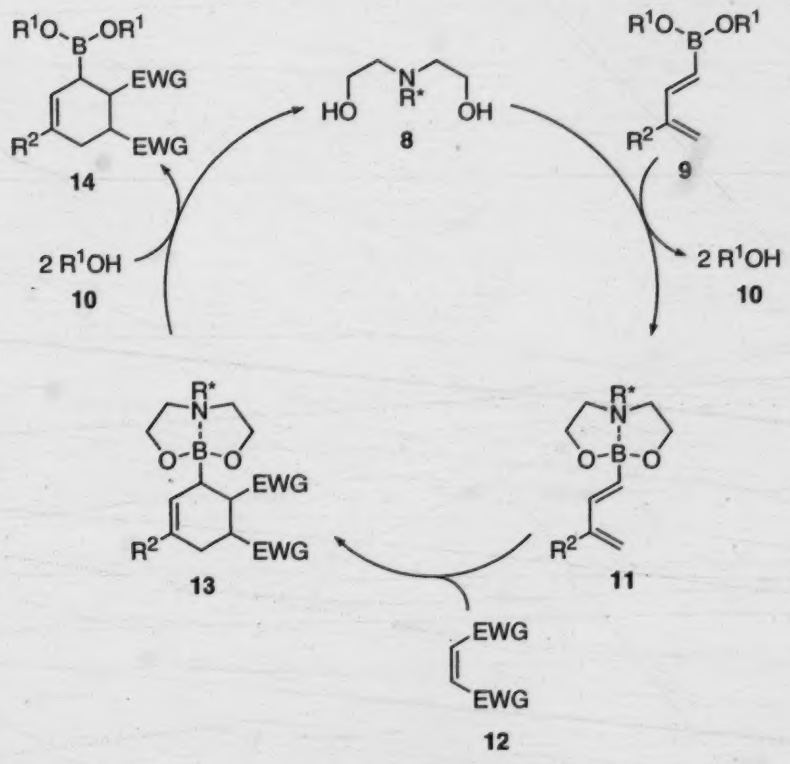
Scheme 6-3

At the outset, in 1998, only the work of Wang[2] had been reported. Thus, we were interested in further exploring the potential of this type of reactions by varying the nature of the diethanolamine derivative to obtain better diastereoselectivity. However, our ultimate goal is to develop an organocatalytic approach in which only a substoichiometric amount of diethanolamine derivative would be necessary. This concept and our work toward this goal are presented in this chapter.

6.2 Cycloadditions of Alkenylboronic Acid-Diethanolamine Adducts

6.2.1 Use of chiral diethanolamine derivatives as organocatalysts

Inspired by the accelerating effect of a diethanolamine derivative in Wang's dienylboronate Diels-Alder reaction,[2] we envisioned an enantioselective organocatalytic approach (Scheme 6-4). In this system, a chiral diethanolamine catalyst **8** would first transesterify a dienylboronate **9**, giving a dienylboronate-diethanolamine adduct **11**. As a result of nitrogen coordination into the empty *p* orbital on boron, it was expected that this adduct (**11**) would be more reactive than the parent dienylboronate **9**. Indeed, this coordination would reduce the delocalization of the diene into this *p* orbital, making the diene more electron-rich and increasing the energy of its HOMO.[6] This adduct (**11**) could then react with a dienophile (**12**) present in the reaction mixture to give a boronate cycloadduct (**13**). The alcohol (**10**) released in the first step (or an added alcohol) could then transesterify the boronate cycloadduct (**13**), thereby yielding the desired enantioenriched product (**14**) and regenerating the diethanolamine catalyst (**8**).



Scheme 6-4

For this catalytic cycle to work, two criteria have to be met:

(1) the diethanolamine-alcohol transesterification processes must occur rapidly under the conditions and solvent used, and

(2) the dienophile must react with the diethanolamine adduct **11** much faster than with the boronate **9** in order to achieve high enantioselectivity.

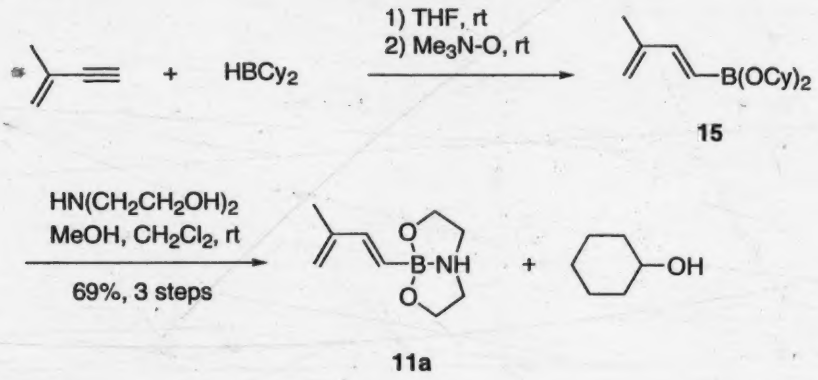
As we have observed previously in our laboratories,[7] the diethanolamine-alcohol transesterification proceeds very quickly for arylboronates and it is thought that dienylboronates would also follow that trend. Our first objective was thus to find

conditions for which the adduct **11** reacts significantly faster than the boronate **9** and in a highly enantioselective fashion.

As a starting point, we first decided to investigate a non-catalytic approach in which several diethanolamine adducts of type **11** would be preformed and reacted directly with a dienophile in order to probe both the reactivity and the intrinsic stereoselectivity of these adducts. Practical advantages of this approach include the accessibility of various chiral aminodiols **8** and the ease of formation of both the dienyl boronate **9** (*via* hydroboration) and the diethanolamine adduct **11**.

6.2.2 Diels-Alder reactions of dienylboronate-diethanolamine adducts

As a preliminary study, we synthesized the simple diethanolamine adduct **11a** (Scheme 6-5). Hydroboration of commercially available 1-methylbut-1-en-3-yne with dicyclohexylborane led to the formation of dienylboronate **15** following *in situ* oxidation with trimethylamine *N*-oxide. The reaction mixture was concentrated and reacted directly with diethanolamine to yield the pure adduct **11a** after crystallization. The fact that the product could be purified by crystallization was of great significance, because the cyclohexanol by-product could not be removed through concentration and its presence may have interfered with the subsequent Diels-Alder reaction.



Scheme 6-5

A series of structurally related boronates (**11b-e**), were then prepared by the same route, using known aminodiols[8] as diethanolamine derivatives (Figure 6-1). Unfortunately, only the adduct **11e** could be crystallized, with the others remaining contaminated by substantial amounts of cyclohexanol.

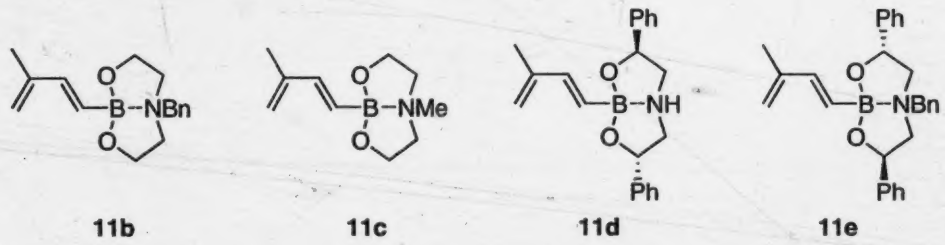


Figure 6-1. Substrates for diastereoselective Diels-Alder reaction

The use of these adducts in Diels-Alder reactions with *N*-phenylmaleimide was then investigated (Table 6-1). To simplify the analysis of the results, the crude products of the Diels-Alder reactions were oxidized to the corresponding alcohol (**5**) under standard conditions.

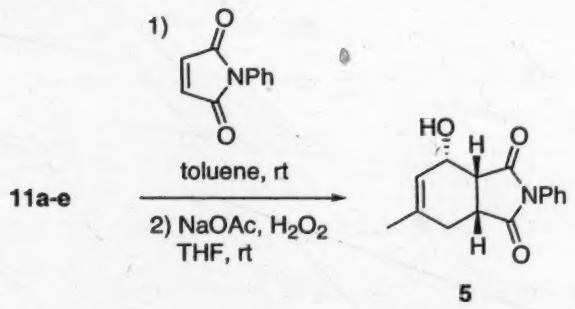


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Table 6-1. Diels-Alder reaction of dienes **11a-e** with *N*-phenylmaleimide[a]

entry	diene	solvent	time	conversion (%)[b]	e.r.[c]
1	**11a**	toluene	14 h	100	-
2	**11b**	toluene	6 d	100	-
3	**11c**	toluene	6 d	100	-
4	**11d**	toluene	16 h	100	1:1.2
5	**11e**	toluene	16 d	80	1.2:1
6	**11e**	CH_2Cl_2	16 d	50	1.2:1
7	**11e**	THF	16 d	50	1.2:1
8	**11e**	MeOH	16 d	20[d]	1.2:1

[a] See section 6.3 for reaction conditions. [b] Measured by integration of cycloadduct vs. starting boronate ^{1}H NMR signals of the crude reaction mixture. [c] As determined by analysis of the Mosher ester derivative.[9] [d] Extensive ring opening of the maleimide resulting from methanolysis was observed.

As can be seen from these results, the diethanolamine derivatives **11b**, **11c**, and **11e**, all bearing a protecting group on the nitrogen, reacted much slower with *N*-phenylmaleimide than the unprotected derivatives **11a** and **11d** (entries 1-5). The nature of the solvent was also found to affect the rate of the reaction, with toluene providing the best results (entries 5-8), although it did not affect the stereochemical outcome. Interestingly, boronates **11d** and **11e** provided the product in the same enantiomeric ratio (entries 4 and 5). All reaction conditions afforded the *endo* product exclusively, as evidenced by ^{1}H NMR analysis.

Although the initial enantiomeric ratios were disappointing, X-ray crystallographic analysis provided some valuable insight for the design of a better diethanolamine derivative. As can be seen in Figure 6-2, the cis [5,5]-bicyclic structure of adduct **11e** adopts a conformation in which the two diastereotopic phenyl groups are almost equidistant from the diene unit. This conformation is expected to result in poor diastereoselectivity because both phenyl groups provide a similar shielding for the diene subunit. On the other hand, the nitrogen protecting group is in a *cis* relationship to the diene unit. This steric hindrance is believed to be the cause of the reduced reactivity of *N*-substituted substrates.

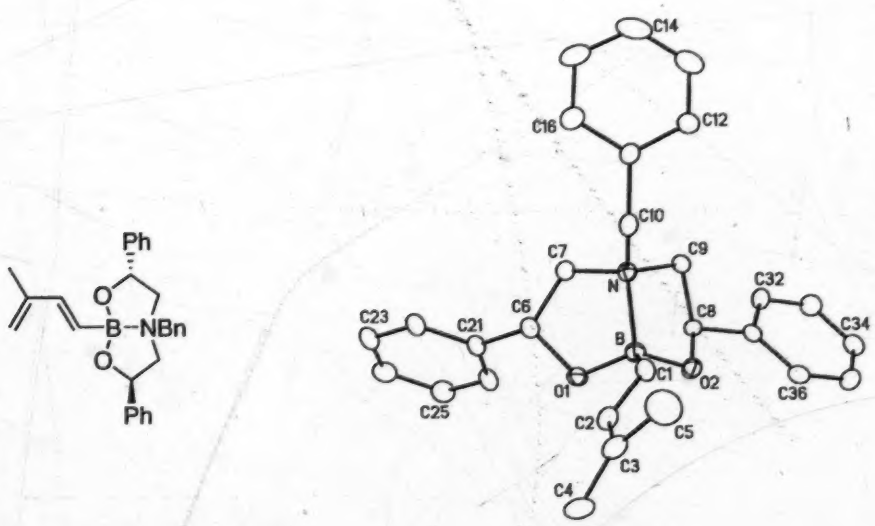
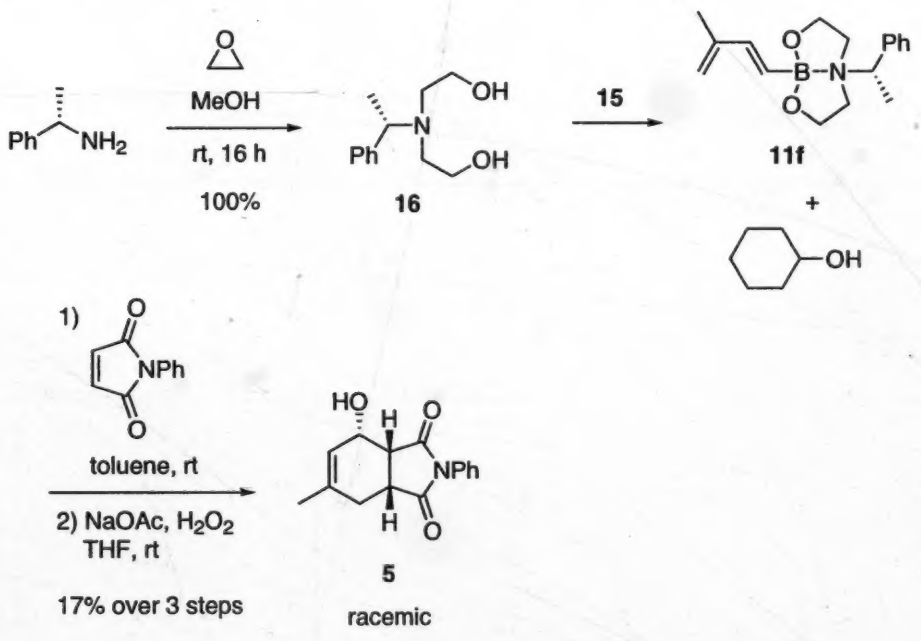


Figure 6-2. ORTEP diagram of boronate **11e**

In view of the close proximity of the nitrogen protecting group to the reacting center, we decided to investigate the use of a diethanolamine derivative bearing a stereogenic center on the protecting group. Dienylboronate-aminodiol adduct **11f** was

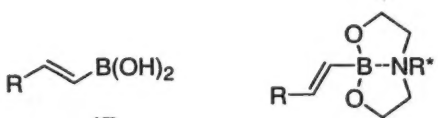
synthesized by first reacting (*S*)-(-)-α-methylbenzylamine with an excess of ethylene oxide (Scheme 6-6). The resulting product **16** was then reacted with dienylboronate **15** (contaminated with cyclohexanol, see Scheme 6-5) to access the adduct **11f**. Unfortunately, all attempts to crystallize this product met with failure and it remained contaminated with substantial amounts of cyclohexanol by-product. The Diels-Alder reaction with *N*-phenylmaleimide was thus performed on the impure diene. In this process, the cycloadduct **5** was obtained as a racemic mixture.



Scheme 6-6

At this stage, it became clear that we needed to access pure boronic acid-diethanolamine adducts that were free of a potentially disrupting coordination from cyclohexanol. We thus decided to turn our attention to reactions involving

alkenylboronate-diethanolamine adducts (**18**) because the synthesis of many alkenylboronic acid (**17**) precursors was known to provide these boronic acids in pure form.

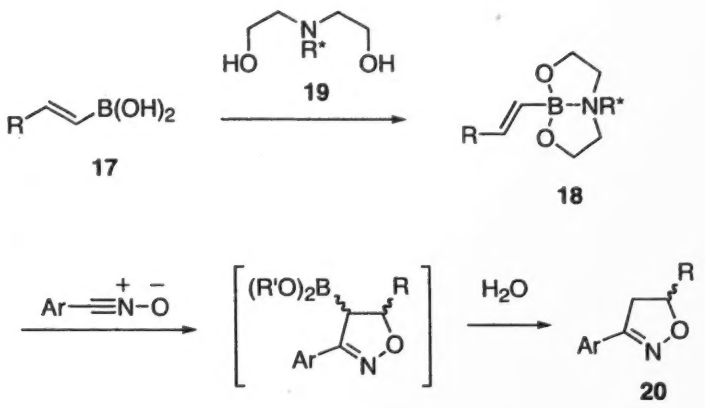


17 **18**

Figure 6-3. Alkenylboronic acid **17** and alkenylboronate **18** diethanolamine adduct **18**

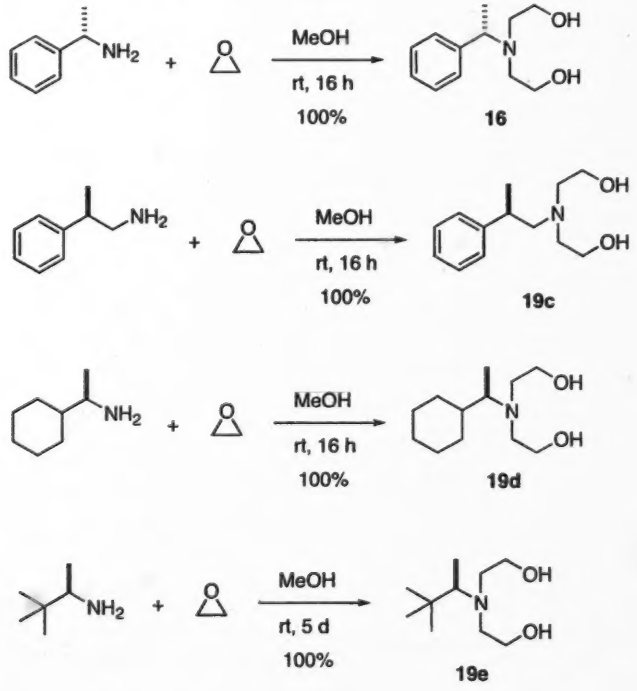
6.2.3 Dipolar cycloaddition reactions of alkenylboronic acid-diethanolamine adducts

In view of the difficulties encountered in making a pure dienylboronic acid, other reactions using alkenylboronate-diethanolamine adducts **18** were envisaged. Because alkenyl boronic acids (**17**) are generally easier to access than dienylboronic acids, 1,3-dipolar cycloadditions using these compounds were investigated (Scheme 6-7). In the event, an alkenylboronate-diethanolamine adduct (**18**) would react with a nitrile oxide to provide an isoxazoline (**20**) following an aqueous work-up.



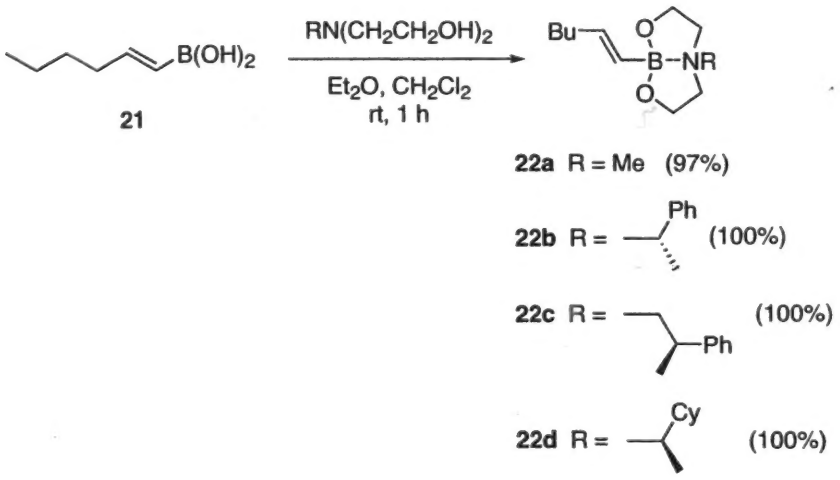
Scheme 6-7

A set of chiral diethanolamine derivatives (**16, 19c-e**) was easily synthesized by condensation of the corresponding primary amines with ethylene oxide, affording the pure products following concentration (Scheme 6-8).



Scheme 6-8

The straightforward synthesis of (*E*)-1-hexenylboronic acid-diethanolamine adducts **22a-d** is presented in Scheme 6-9. In a typical experiment, a solution of the aminodiol in dichloromethane was added to a solution of the boronic acid in diethyl ether and then concentrated to afford the desired adduct.



Scheme 6-9

These aminodiol-boronic acid adducts **22a-d** were then subjected to a 1,3-dipolar cycloaddition with benzonitrile oxide (generated *in situ* from phenyl oximoyl chloride and triethylamine), and the results are summarized in Table 6-2.

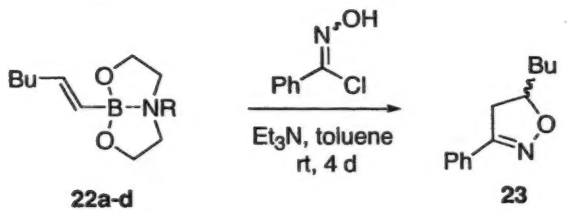


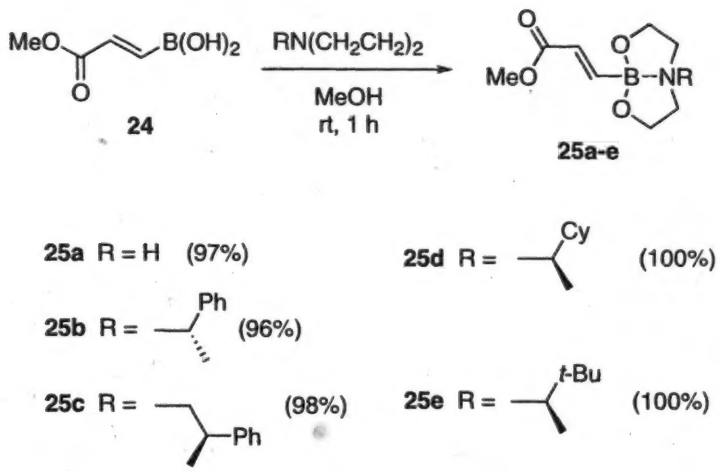
Table 6-2. Dipolar cycloadditions of (*E*)-1-hexenylboronic acid derivatives with benzonitrile oxide[a]

entry	alkenylboronate	yield (%)[b]	ee (%)[c]
1	**22a**	3	-
2	**22b**	36	25
3	**22c**	30	4
4	**22d**	19	2

[a] See section 6.3 for reaction conditions. [b] Yield of isolated, analytically pure product. [c] As determined by chiral HPLC analysis (see section 6.3).

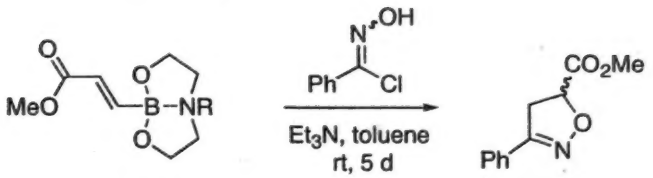
As can be seen from these results, derivative **22b** provided the best yield and the best enantioselectivity (entry 2). Despite this encouraging result, there needed to be much improvement to make this process useful.

We then turned our attention to (*E*)-2-(methoxycarbonyl)vinylboronic acid-diethanolamine adducts, easily accessible from our vinylboronic acid preparation (Chapter 3). Derivatives **25a-e** were thus prepared in a similar fashion to **22** (Scheme 6-10).



Scheme 6-10

The aminodiol-boronic acid adducts **25a-e** were also subjected to a 1,3-dipolar cycloaddition with benzonitrile oxide, and the results are summarized in Table 6-3. At the same time that we were working on this project, an article by Marsden and co-workers was published which reported results similar to the ones in entry 2.[10] In their hands, substrate **25b** was also found to provide the best enantiomeric ratio for this reaction.



25a-d **26**

Table 6-3. Dipolar cycloadditions of (*E*)-2-(methoxycarbonyl)vinyl-boronic acid derivatives with benzonitrile oxide[a]

entry	alkenylboronate	yield (%)[b]	ee (%)[c]
1	**25a**	15	-
2	**25b**	14	69
3	**25c**	22	29
4	**25d**	8	0
5	**25e**	32	12

[a] See section 6.3 for reaction conditions. [b] Yield of isolated, analytically pure product. [c] As determined by chiral HPLC analysis (see section 6.3).

As these results show, substitution with chiral protecting groups on the nitrogen atom have a stronger directing effect in this reaction than substitution on the ethanol side chains. Unfortunately, the reduced reactivity of nitrogen-substituted alkenylboronate-diethanolamine adducts is reflected in the low yields reported for this reaction.

In summary, the significant decrease in reactivity of the nitrogen-substituted alkenylboronate-diethanolamine adducts compared to the parent non-substituted adducts limits the possibility of devising a catalytic system, as was originally planned. Despite the knowledge gained and the interesting results ontained, there did not appear to be good potential for this project to achieve the desired goal. It was therefore decided to abandon the project at this stage.

On the positive side, our involvement with this project and the difficulties encountered in the purification of some boronic acids highlighted the need for a solid support which could selectively and efficiently immobilize boronic acids. This concept led to the development of DEAM-PS, as described in Chapter 2.

6.3 Experimental

6.3.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. NMR spectra were recorded on a Bruker AM 300, Bruker AM 200, Varian INOVA-300, INOVA-400 or INOVA-500 instrument. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards for chemical shifts. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 instrument. Optical rotations were recorded using Perkin-Elmer PE-241. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 system. The enantiomeric excess for compound **5** was determined using integration of the ^1H NMR signals of the corresponding Mosher ester derivative.[9] The enantiomeric excess for compounds **23** and **26** was determined using an HP 1100 HPLC system. Chiralcel AD-RH column was purchased from Chiral Technologies Inc. Melting

points were determined using a Gallenkamp apparatus. X-ray crystallography was performed using a Bruker P4/RA/SMART 1000 CCD diffractometer.

6.3.2 Synthesis of (*E*)-2-(1-methylethenyl)vinylboronate adducts 11a-f and their use in Diels-Alder reactions

Dicyclohexyl (*E*)-2-(1-methylethenyl)vinylboronate (15)

To a solution of borane-dimethyl sulfide complex (1.40 mL, 14 mmol) in THF (20 mL) at 0 °C was added cyclohexene (2.84 mL, 28 mmol). The solution was stirred at 0 °C for 10 minutes, then at room temperature for 1 hour, upon which a white precipitate was formed. The suspension was then cooled to 0 °C and 2-methyl-but-1-en-3-yne (1.33 mL, 14 mmol) was added dropwise. The suspension was stirred at 0 °C for 30 minutes, then at room temperature for 30 minutes, upon which the white precipitate disappeared. The solution was cooled to 0 °C and trimethylamine *N*-oxide dihydrate (3.11 g, 28 mmol) was added in one portion. The mixture was stirred at 0 °C for 30 minutes, then at room temperature for 16 hours. The resulting solution was concentrated *in vacuo* to obtain boronate **15** as an unstable yellow oil, which was used directly in the next step.

Typical procedure for the synthesis of vinylboronate adducts 11a-e:

(*E*)-2-(1-Methylethenyl)vinylboronic acid-diethanolamine adduct (11a)

Boronate **15** (910 mg, 3.30 mmol) was dissolved in dichloromethane (10 mL) and a solution of diethanolamine (346 mg, 3.30 mmol) in methanol (1 mL) was added. The mixture was stirred at room temperature for 3 hours, then concentrated *in vacuo*. To the resulting yellow oil was added Et_2O (20 mL) and the resulting precipitate was filtered to

yield adduct **11a** as a pale yellow powder (481 mg, 69%) contaminated with residual cyclohexanol. An analytically pure sample was obtained through recrystallization (dichloromethane/hexanes), colorless solid: m.p. 100-107 °C(dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J = 18.0 Hz, 1H), 5.72 (d, J = 18.0 Hz, 1H), 4.91 (s, 2H), 4.39 (br s, 1H), 4.10-3.80 (m, 4H), 3.40-3.10 (m, 2H), 2.90-2.70 (m, 2H), 1.82 (d, J = 1.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 141.5, 114.8, 63.0, 51.3, 18.5 ; HRMS (EI, *m/z*) calcd for $C_9H_{16}BNO_2$ 181.12741, found 181.12741.

(*E*)-2-(1-Methylethenyl)vinylboronic acid-*N*-benzyl-diethanolamine adduct (11b)

White solid, 49% yield: m.p. 122-126 °C(dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 3H), 7.33-7.28 (m, 2H), 6.80 (d, J = 17.9 Hz, 1H), 5.74 (d, J = 17.8 Hz, 1H), 5.00 (s, 1H), 4.97 (s, 1H), 4.04 (t, J = 6.1 Hz, 4H), 3.81 (s, 2H), 3.40-2.60 (m, 4H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 143.5, 132.9, 130.8, 129.1, 129.0, 115.4, 62.4, 62.1, 56.6, 18.5; FTIR (microscope) 3500-3200, 3057, 2983, 1593, 1075 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{16}H_{22}BNO_2$ 271.17435, found 271.17445.

(*E*)-2-(1-Methylethenyl)vinylboronic acid-*N*-methyl-diethanolamine adduct (11c)

Yellow oil (impure): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, J = 17.9 Hz, 1H), 5.61 (d, J = 17.9 Hz, 1H), 4.94 (s, 1H), 4.92 (s, 1H), 4.10-3.80 (m, 4H), 4.10-3.80 (m, 4H), 3.15-2.85 (m, 4H), 2.60 (s, 3H), 1.84 (s, 3H).

(*E*)-2-(1-Methylethenyl)vinylboronic acid-(2*S*,2'*S*)-2,2'-diphenyl-diethanolamine adduct (11d)

White solid (impure): m.p. 210-220 °C(dec.); $[\alpha]^{25}_{D}$ = +77.1° (*c* = 0.99, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.29 (m, 10H), 6.81 (d, *J* = 18.0 Hz, 1H), 5.88 (d, *J* = 18.0 Hz, 1H), 5.22 (ddd, *J* = 18.0, 10.6, 3.9 Hz, 2H), 4.99 (s, 2H), 3.78-3.70 (m, 1H), 3.02-2.94 (m, 1H), 2.86-2.80 (m, 1H), 2.72-2.65 (m, 1H), 1.88 (s, 3H); FTIR (microscope) 3194, 3087, 2913, 1594, 1454, 1043 cm^{-1}; HRMS (EI, *m*/z) calcd for $C_{21}H_{24}BNO_2$ 333.19000, found 333.19016.

(*E*)-2-(1-Methylethenyl)vinylboronic acid-*N*-benzyl-(2*R*,2'*R*)-2,2'-diphenyl-diethanolamine adduct (11e)

White solid, 63% yield: m.p. 167-172 °C(dec.); $[\alpha]^{25}_{D}$ = -29.9° (*c* = 1.77, THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.45 (m, 4H) 7.45-7.25 (m, 11H), 7.00 (d, *J* = 17.9 Hz, 1H), 5.91 (d, *J* = 17.8 Hz, 1H), 5.22 (ddd, *J* = 18.0 Hz, 10.7 Hz, 4.0 Hz, 2H), 5.03 (s, 1H), 5.00 (s, 1H), 4.01 (d, *J* = 14.3 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 3.62 (dd, *J* = 12.3 Hz, 4.6 Hz, 1H), 2.95 (dd, *J* = 11.3 Hz, 3.9 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.54 (t, *J* = 11.4 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 143.7, 141.2, 140.8, 132.8, 131.0, 129.3, 129.1, 128.5, 128.5, 127.8, 127.8, 126.1, 125.8, 115.6, 73.4, 73.0, 65.9, 60.9, 60.6, 18.7; FTIR (microscope) 3032, 2973, 2843, 1593, 1450, 1108 cm^{-1}; HRMS (ES, *m*/z) calcd for $C_{28}H_{31}BNO_2$ 424.2448, found 424.2447.

(*E*)-2-(1-Methylethenyl)vinylboronic acid-*N*-[(*S*)-1-Phenylethyl]-diethanolamine adduct (11f)

Yellow oil (impure): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 6.81 (d, *J* = 18.0 Hz, 1H), 5.83 (d, *J* = 17.9 Hz, 1H), 5.00 (s, 1H), 4.97 (s, 1H), 4.07 (q, *J* = 6.8 Hz, 1H), 4.10-3.80 (m, 4H), 3.20-2.60 (m, 4H), 1.89 (s, 3H), 1.58 (d, *J* = 6.9 Hz, 3H); HRMS (EI, *m/z*) calcd for $C_{17}H_{24}BNO_2$ 285.19000, found 285.18906.

Typical procedure for the reaction of adducts 11a-e with *N*-phenylmaleimide: Reaction of adduct 11e with *N*-phenylmaleimide

To a solution of adduct **11e** (15 mg, 0.04 mmol) in THF (2.5 mL) was added *N*-phenylmaleimide (6 mg, 0.04 mmol). The resulting solution was stirred at room temperature for 16 days, then concentrated *in vacuo*. The crude cycloaddition product was then analyzed by ^{1}H NMR to measure the conversion. The crude mixture was then dissolved in THF (2 mL) and cooled down to 0 °C. An aqueous solution of sodium acetate (6 μL of a 3 M solution, 0.02 mmol) was then added, followed by an aqueous solution of hydrogen peroxide (10 μL of a 30% solution, 0.11 mmol). The mixture was stirred at 0 °C for 2 hours, then diluted with Et_2O (5 mL), and washed with H_2O (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to obtain a yellow solid. Flash chromatography on silica gel (50% EtOAc/Hexanes) afforded pure cycloadduct **5**[3] as a white solid (5 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.35 (m, 3H), 7.24-7.19 (m, 2H), 5.78 (ddd, *J* = 3.5, 1.7, 1.7 Hz, 1H), 4.52 (br s, 1H), 3.40-3.20 (m, 3H), 2.64 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.31 (dd, *J* = 16.1, 8.1 Hz, 1H), 1.79 (s, 3H).

General procedure for the synthesis of aminodiols 16 and 19c-d:

In a 10-mL round bottom flask, the amine (4 mmol) was dissolved in MeOH (3 mL). Ethylene oxide (2 mL, ca. 10 equiv.) was quickly added and the flask was stoppered with a septum. The solution was stirred for 16 hours at room temperature and then concentrated *in vacuo* to afford aminodiols **16, 19c-d**.

***N*-[(*S*)-1-Phenylethyl]-diethanolamine (16)**

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = +30.2° (*c* = 1.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.30 (m, 3H), 7.26-7.23 (m, 2H), 3.96 (q, *J* = 6.9 Hz, 1H), 3.62-3.48 (m, 4H), 2.72 (ddd, *J* = 13.6, 5.6, 4.7 Hz, 2H), 2.60 (ddd, *J* = 13.6, 6.6, 4.8 Hz, 2H), 1.40 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.3, 127.9, 127.1, 60.2, 59.3, 52.1, 15.1; FTIR (neat) 3362, 3027, 2968, 1452, 1046 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{12}H_{19}NO_2$ 209.14159, found 209.14161.

***N*-[(*R*)-2-Phenylpropyl]-diethanolamine (19c)**

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = +25.9° (*c* = 1.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.31 (m, 2H), 7.29-7.18 (m, 3H), 3.50-3.43 (m, 4H), 3.00-2.89 (m, 1H), 2.74-2.60 (m, 4H), 2.59-2.49 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.8, 128.6, 127.1, 126.5, 62.9, 59.4, 56.5, 38.6, 19.9; FTIR (neat) 3377, 3027, 2956, 1452, 1041 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{13}H_{21}NO_2$ 223.15723, found 223.15638

***N*-[(*R*)-1-Cyclohexylethyl]-diethanolamine (19d)**

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = -86.6° (*c* = 2.13, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65-3.49 (m, 4H), 2.69 (ddd, *J* = 13.5, 9.0, 5.1 Hz, 2H), 2.50 (ddd, *J* = 13.5, 3.9, 3.9 Hz, 2H), 2.44 (br s, 2H), 2.29 (dq, *J* = 9.3, 6.6 Hz, 1H), 2.19-2.09 (m, 1H), 1.77-1.59 (m, 4H), 1.31-1.07 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91-0.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 61.1, 60.4, 51.9, 41.0, 31.3, 30.7, 26.6, 26.5, 26.2, 11.0; FTIR ($CHCl_3$) 3354, 2921, 2850, 1448, 1034 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{12}H_{25}NO_2$ 215.18852, found 215.18784; Anal. Calcd for $C_{12}H_{25}NO_2$: C 66.94, H 11.70, N 6.50; found: C 65.90, H 11.95, N 6.43.

***N*-[(1*R*)-1,2,2-trimethylpropyl]-diethanolamine (19e)**

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = -89.4° (*c* = 2.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68-3.51 (m, 4H), 2.73 (ddd, *J* = 13.9, 9.6, 4.2 Hz, 2H), 2.60-2.40 (br s, 2H), 2.47 (ddd, *J* = 13.6, 3.5, 3.5 Hz, 2H), 2.29 (q, *J* = 7.0 Hz, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 65.1, 60.4, 54.0, 35.2, 27.8, 8.0; FTIR (neat) 3354, 2951, 1462, 1240, 1038 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{10}H_{24}NO_2$ 190.18016, found 190.17995.

(*E*)-1-Hexenylboronic acid (21)[11]

To a solution of 1-hexyne (3.0 mL, 26.1 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added dibromoborane-methyl sulfide complex (23.5 mL of a 1.0 M solution in CH_2Cl_2, 23.5 mmol) over a period of 15 minutes. The solution was stirred at 0 °C for 20 minutes, then at room temperature for 3 hours. The resulting a green solution was concentrated

under reduced pressure, then added slowly at 0 °C to a stirred solution of sodium hydroxide (52.2 mL of a 1.0 M solution in water, 52.2 mmol). The resulting suspension was vigorously at 0 °C for 30 minutes, then at room temperature for 10 minutes. Diethyl ether (ca. 40 mL) was added to dissolve the white precipitate, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to obtain 3.00 g (100 %) of boronic acid **21** as a white solid: ^{1}H NMR (CD_3OD, 300 MHz) d 6.52 (dt, J = 17, 7 Hz, 1H), 5.55 (d, J = 18 Hz, 1H), 2.15 (q, J = 7 Hz, 2H), 1.37-1.23 (m, 4H), 0.91 (t, J = 7 Hz, 3H).

(*E*)-2-(Methoxycarbonyl)vinylboronic acid (24)

To a stirred solution of borane-dimethylsulfide complex (1.0 mL, 10 mmol) in 2 mL of tetrahydrofuran at 0 °C, was added (1*R*)-(+)-α-pinene (3.65 mL, 23 mmol) dropwise. The solution was warmed up to room temperature, then stirred for 2 hours, upon which a white precipitate was formed. The reaction mixture was cooled to 0 °C, then methyl propiolate (1.02 mL, 11.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour, upon which it became a clear yellow solution. Acetaldehyde (ca. 6 mL, 100 mmol) was added slowly and the solution was stirred at 0 °C for 1 hour. The reaction vessel was fitted with a condenser and the solution was heated at 45 °C for 16 hours. The resulting solution was cooled to 0 °C, then water (15 mL) was added and the reaction was stirred at 0 °C for 2 hours. The resulting mixture was extracted with diethyl ether (5 × 10 mL) and concentrated directly until dryness. The yellow solid was triturated with cold dichloromethane (4 × 15 mL) and dried under

vacuum, affording 964 mg (74%) of boronic acid **24** as a white solid: mp 121-128 °C. ^{1}H NMR (500 MHz, CD_3OD + 5% D_2O) δ 6.78 (d, J = 17.9 Hz, 1H), 6.48 (d, J = 18.1 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD + 5% D_2O) δ 168.6, 136.3, 52.4; FTIR (microscope) 3427, 3321, 2953, 1706 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_4H_7O_4B$ 130.0437 found 130.0438.

Alkenylboronic acid-diethanolamine adducts 22a-d and 25a-e

General procedure

To a stirred solution of boronic acid **21** or **24** (1.0 mmol) in methanol or diethyl ether (1 mL) at room temperature, was added a solution of aminodiol (1.0 mmol) in methanol or dichloromethane (1 mL). The mixture was stirred for 10 minutes, then concentrated to obtain alkenylboronic acid-diethanolamine adducts **22a-d**, **25a-e**

(*E*)-1-Hexenylboronic acid-*N*-methyl-diethanolamine adduct (22a)

Colorless oil, 97% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.05 (dt, J = 17.4, 6.4 Hz, 1H), 5.35 (dt, J = 17.4, 1.5 Hz, 1H), 4.05-3.30 (m, 4H), 3.10-2.80 (m, 4H), 2.58 (s, 3H), 2.10-2.00 (m, 2H), 1.40-1.20 (m, 4H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.7, 61.6, 60.6, 47.1, 35.3, 31.4, 22.3, 14.0; FTIR (microscope) 2956, 2925, 2872, 1637, 1459 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{11}H_{22}BNO_2$ 211.17436, found 211.17458.

(*E*)-1-Hexenylboronic acid-*N*-[(*S*)-1-phenylethyl]-diethanolamine adduct (22b)

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = -11.5° (*c* = 1.69, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.28 (m, 5H), 6.17 (dt, *J* = 17.2, 6.3 Hz, 1H), 5.58 (d, *J* = 17.4 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 1H), 4.05-3.80 (m, 4H), 3.30-2.60 (m, 2H), 2.85-2.65 (m, 2H), 2.20-2.10 (m, 2H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.45-1.25 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.9, 139.3, 128.9, 128.7, 128.3, 65.2, 63.1, 60.2, 35.4, 31.4, 22.3, 18.3, 14.0; FTIR (microscope) 3028, 2956, 2928, 2873, 1636, 1454 cm^{-1}.

(*E*)-1-Hexenylboronic acid-*N*-[(*R*)-2-phenylpropyl]-diethanolamine adduct (22c)

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = -14.5° (*c* = 1.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.18 (m, 5H), 6.03 (dt, *J* = 17.4, 6.4 Hz, 1H), 5.37 (dt, *J* = 17.4, 1.4 Hz, 1H), 3.90-3.75 (m, 4H), 3.20-3.08 (m, 1H), 3.10-2.82 (m, 2H), 3.00-2.20 (m, 4H), 2.10 (qd, *J* = 7.0, 1.2 Hz, 2H), 1.42-1.30 (m, 4H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 143.2, 129.1, 128.6, 127.1, 66.1, 62.8, 56.5, 37.8, 35.3, 31.4, 22.6, 22.3, 14.0; FTIR (microscope) 3027, 2957, 2927, 2871, 1637, 1453 cm^{-1}.

(*E*)-1-Hexenylboronic acid-*N*-[(*R*)-1-cyclohexylethyl]-diethanolamine adduct (22d)

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = -18.7° (*c* = 1.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.04 (dt, *J* = 17.4, 6.5 Hz, 1H), 5.43 (dt, *J* = 17.4, 1.5 Hz, 1H), 4.05-3.95 (m, 4H), 3.10-2.80 (m, 5H), 2.06 (qd, *J* = 6.4, 1.4 Hz, 2H), 1.80-1.60 (m, 4H), 1.50-1.40 (m, 1H), 1.40-1.00 (m, 10H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.2, 65.7, 63.3, 39.4, 35.3, 31.8, 31.3, 27.6, 26.7, 26.3, 22.3, 14.0,

11.5; FTIR ($CHCl_3$) 2924, 2852, 1634, 1448 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{18}H_{34}BNO_2$ 307.26825, found 307.26654.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid-diethanolamine adduct (25a)

White solid, 100% yield: m.p. 175-179 °C(dec.); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, *J* = 17.9 Hz, 1H), 6.26 (d, *J* = 17.9 Hz, 1H), 5.18 (br s, 1H), 4.10-3.98 (m, 2H), 3.96-3.86 (m, 2H), 3.69 (s, 3H), 3.35-3.22 (m, 2H), 2.87-2.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 128.4, 63.1, 51.3, 51.2; FTIR (microscope) 3088, 2947, 2872, 1713, 1442 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_8H_{15}BNO_4$ 200.10887, found 200.10880; Anal. Calcd for $C_8H_{14}BNO_4$: C 48.28, H 7.09, N 7.04; found: C 48.04, H 7.25, N 6.79.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid-*N*-[(*S*)-1-Phenylethyl]-diethanolamine adduct (25b)

Colorless oil, 96% yield: $[\alpha]^{25}_D$ = -61.8° (*c* = 1.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.28 (m, 5H) 7.22 (d, *J* = 17.7 Hz, 1H), 6.43 (d, *J* = 17.7 Hz, 1H), 4.06 (q, *J* = 6.8 Hz, 1H), 4.10-3.90 (m, 4H), 3.73 (s, 3H), 3.10-2.40 (m, 4H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 138.2, 130.8, 129.1, 129.1, 128.4, 65.5, 63.0, 51.3, 18.2; FTIR (microscope) 2984, 2949, 2877, 1713, 1456 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{16}H_{22}BNO_4Na$ 326.15341, found 326.15351.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid-*N*-[(*R*)-2-Phenylpropyl]-diethanolamine adduct (25c)

Colorless oil, 98% yield: $[\alpha]^{25}_{D}$ = -57.7° (*c* = 1.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.16 (m, 5H), 7.02 (d, *J* = 17.8 Hz, 1H), 6.32 (d, *J* = 17.8 Hz, 1H), 4.05-3.90 (m, 2H), 3.85-3.60 (m, 2H), 3.72 (s, 3H), 3.22-3.08 (m, 1H), 3.10-2.90 (m, 2H), 2.72-2.30 (m, 4H), 1.27 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 144.2, 130.4, 129.3, 127.5, 127.0, 65.5, 62.9, 58.4, 51.3, 37.8, 22.7; FTIR (microscope) 2966, 2873, 1716, 1253 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{17}H_{25}BNO_4$ 318.18712, found 318.18710.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid-*N*-[(*R*)-1-cyclohexylethyl]-diethanolamine adduct (25d)

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = +38.6° (*c* = 1.44, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, *J* = 17.8 Hz, 1H), 6.33 (d, *J* = 17.8 Hz, 1H), 4.10-3.90 (m, 4H), 3.68 (s, 3H), 3.30-2.80 (m, 5H), 1.95-1.60 (m, 5H), 1.31-0.92 (m, 6H), 1.18 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.8, 130.3, 66.3, 63.4, 51.2, 39.5, 31.9, 27.7, 26.5, 26.1, 11.6; FTIR ($CHCl_3$) 2927, 2854, 1717, 1253 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{16}H_{29}BNO_4$ 310.21841, found 310.21850.

(*E*)-2-(Methoxycarbonyl)vinylboronic acid-*N*-[(1*R*)-1,2,2-trimethylpropyl]-diethanolamine adduct (25e)

Colorless oil, 100% yield: $[\alpha]^{25}_{D}$ = +38.5° (*c* = 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, *J* = 17.4 Hz, 1H), 6.34 (d, *J* = 18.0 Hz, 1H), 4.10-3.90 (m, 2H),

3.80-3.60 (m, 2H), 3.71 (s, 3H), 3.35-3.18 (m, 1H), 2.98-2.84 (m, 2H), 2.78-2.56 (m, 1H), 1.64-1.46 (m, 1H), 1.26-1.10 (m, 3H), 1.04 (s, 9H); FTIR ($CHCl_3$) 2952, 2871, 1717, 1245 cm^{-1}; HRMS (ES, *m/z*) calcd for $C_{14}H_{27}BNO_4$ 284.20277, found 284.20248.

3-Phenyl-5-butyl-Δ^2-isoxazoline (23)[12]

White solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.62 (m, 1H), 7.53-7.49 (m, 1H), 7.47-7.41 (m, 1H), 7.41-7.35 (m, 2H), 4.72 (dddd, *J* = 16.3, 10.3, 6.8, 6.0 Hz, 1H), 3.37 (dd, *J* = 16.5, 10.3 Hz, 1H), 2.95 (dd, *J* = 16.4, 8.3 Hz, 1H), 1.86-1.72 (m, 1H), 1.68-1.56 (m, 1H), 1.50-1.30 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H).

3-Phenyl-5-carbomethoxy-Δ^2-isoxazoline (26)[10]

White solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69-7.64 (m, 2H), 7.43-7.36 (m, 3H), 5.18 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.81 (s, 3H), 3.64 (d, *J* = 7.6 Hz, 1H), 3.63 (d, *J* = 10.6 Hz, 1H).

6.4 References

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Chapter 7

Thesis Conclusions

This thesis describes research aimed at the synthesis and applications of boronic acids and boronic esters. Over the course of these studies, we were able to develop two different strategies for the synthesis and purification of aryl- and alkenylboronic acids. Additionally, various boronic acids obtained through these strategies were applied to the Suzuki resin-to-resin transfer reaction, the Lewis-acid catalyzed asymmetric addition of allylboronates to aldehydes, and the cycloaddition reactions of boronic acid-diethanolamine adducts.

The development of DEAM-PS, the first solid support for the selective immobilization and derivatization of boronic acids, provides a straightforward synthesis of various highly functionalized arylboronic acids. Indeed, the use of DEAM-PS resin greatly facilitates access to arylboronic acid derivatives that can be otherwise difficult to synthesize and isolate by solution phase methods. Specifically, DEAM-PS allows for the derivatization of arylboronic acids through nucleophilic substitution, reductive amination, amide coupling, anilide, urea and thiourea formation, as well as Ugi four-component coupling. Significantly, all products obtained in this way show a very high degree of purity, without the need for any additional purification. The use of DEAM-PS proved instrumental in the resin-to-resin Suzuki coupling reaction developed subsequently. Since the development of DEAM-PS, there has been a lot of progress in the area of silica-

supported reagents and linkers. It would be interesting to explore the use of DEAM-silica in similar applications and determine the advantages, if any, of silica-supported reagents for the immobilization of boronic acids.

During the course of our investigations on the cycloaddition reactions of boronic acid-diethanolamine derivatives, we needed to access alkenylboronic acids of high purity. As most available methods for the synthesis of alkenylboronates provide the corresponding alkenylboronic esters, we developed a convenient and general method for the synthesis of functionalized *E*-alkenylboronic acids. This method relies on the hydroboration of alkynes using diisopinocampheylborane, followed by an oxidative/hydrolytic work-up and trituration in hexanes. The use of diisopinocampheylborane in this context has the advantage of generating a volatile alcohol by-product, ethanol. Indeed, most common hydroboration reagents generate a non-volatile alcohol or diol as a by-product, thus making the purification of the boronic acid product very difficult. This new procedure has proven very useful for the synthesis of boronic acid-diethanolamine adducts of high purity. Significantly, this method tolerates a wide range of functionalities on the alkyne substrate, giving access to boronic acids bearing useful functional groups.

The use of DEAM-PS-supported boronic acids in the Suzuki resin-to-resin transfer reaction illustrates well the advantages of using a two-resin system. The possibility of a convergent solid phase synthesis and eventual coupling of fragments constitutes probably the most important advantage. Indeed, such a strategy becomes

essential when faced with a linear SPOS strategy that involves incompatible reaction conditions. Additionally, a two-resin system such as the one developed circumvents the need for time-consuming cleavage and transfer operations. To test the usefulness of such a system, a small model library of biphenyl compounds was synthesized in a concise fashion.

The discovery that Lewis acids catalyze the addition of allylboronates to aldehydes triggered the development of a general method for the asymmetric version of this reaction. We found that the use of Hoffmann's camphor-derived boronates, under Sc(III) catalysis, provides a general entry to a wide variety of homoallylic alcohols. The importance of this methodology is underlined by the previous lack of a method for the addition of various allylboronates using stable reagents to generate homoallylic products in very high diastereo- and enantiomeric excesses. To improve on this methodology, it would be of great importance to develop a catalytic asymmetric version of these reactions. Ideally, a catalytic amount of a *chiral* Lewis acid would mediate the addition of *achiral* allylboronates to aldehydes. Preliminary studies in the Hall laboratory in this area have not yet succeeded in providing addition products of high enantiomeric purity. Another variation on this theme, which could prove useful, is the extension of this method to the addition of allylboronates to other carbonyl equivalents, namely imines and ketones. The successful application of our methodology to these substrates would constitute a significant advance because there are relatively few asymmetric methods available for these transformations.

Appendix

X-Ray Crystallography Report of Boronate 11e

University of Alberta Department of Chemistry
X-Ray Crystallography Laboratory

STRUCTURE REPORT

XCL Code: DGH9907
Date: 13 December 1999
Compound: $PhCH_2N(CH_2CHPhO)_2BCH{=}CHC(Me){=}CH_2$
Formula: $C_{28}H_{30}BNO_2$
Supervisor: D. G. Hall

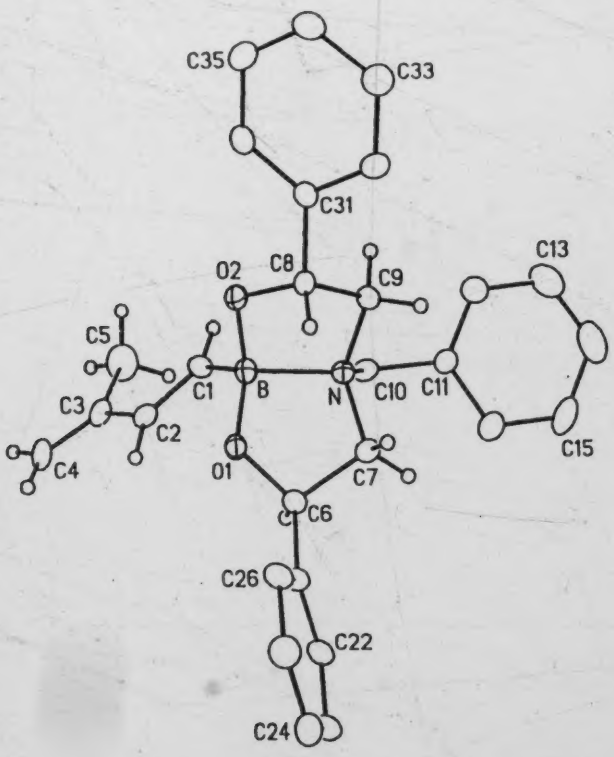

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{28}H_{30}BNO_2$
formula weight	423.34
crystal dimensions (mm)	0.31 × 0.14 × 0.08
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	12.423 (3)
b (Å)	13.369 (3)
c (Å)	14.345 (3)
V (Å^3)	2382.4 (9)
Z	4
ρ_{calcd} (g cm^{-3})	1.180
μ (mm^{-1})	0.073
B. Data Collection and Refinement Conditions	
diffractometer	Bruker P4/RA/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ϕ rotations (0.3°) / ω scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	52.90
total data collected	11851 ($-14 \le h \le 15$, $-15 \le k \le 16$, $-8 \le l \le 17$)
independent reflections	4884
number of observations (*NO*)	1671 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	*SADABS*
range of transmission factors	0.9677–0.5589
data/restraints/parameters	4884 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 290
Flack absolute structure parameter[e]	4 (2)
goodness-of-fit (*S*)[f]	0.794 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0534
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1091
largest difference peak and hole	0.183 and –0.160 e Å^{-3}

[a]Obtained from least-squares refinement of 2438 centered reflections.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted R-factors wR_2 and all goodnesses of fit S are based on F_o^2; conventional R-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. R-factors based on F_o^2 are statistically about twice as large as those based on F_o, and R-factors based on ALL data will be even larger.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. In cases such as this one, where the Flack parameter's value is far removed from the 0–1 range, the absolute configuration cannot be assigned on the basis of the X-ray results alone, but is determined from the known stereochemistry of the starting materials.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0236P)^2]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.1527(2)	0.5542(2)	0.22949(18)	0.0406(8)*
O2	0.0868(2)	0.4968(2)	0.08100(18)	0.0432(8)*
N	0.2793(3)	0.5340(2)	0.0992(2)	0.0334(9)*
C1	0.1777(4)	0.3708(4)	0.1840(3)	0.0452(13)*
C2	0.1535(3)	0.3381(3)	0.2703(3)	0.0423(12)*
C3	0.1531(4)	0.2339(4)	0.3050(4)	0.0467(13)*
C4	0.1078(3)	0.2149(4)	0.3859(3)	0.0555(15)*
C5	0.2022(4)	0.1571(3)	0.2460(4)	0.084(2)*
C6	0.2550(4)	0.5936(3)	0.2540(3)	0.0376(12)*
C7	0.3053(3)	0.6205(3)	0.1603(2)	0.0401(12)*
C8	0.1154(3)	0.5802(3)	0.0253(3)	0.0358(12)*
C9	0.2350(3)	0.5639(3)	0.0068(3)	0.0345(11)*
C10	0.3727(3)	0.4639(3)	0.0904(3)	0.0419(12)*
C11	0.4661(4)	0.5030(3)	0.0330(3)	0.0376(11)*
C12	0.4703(4)	0.4846(4)	-0.0608(3)	0.0509(14)*
C13	0.5508(5)	0.5232(5)	-0.1144(4)	0.0750(19)*
C14	0.6313(5)	0.5782(5)	-0.0760(5)	0.082(2)*
C15	0.6330(4)	0.5942(4)	0.0191(5)	0.0670(16)*
C16	0.5497(4)	0.5570(3)	0.0740(3)	0.0520(13)*
C21	0.2442(4)	0.6816(3)	0.3205(3)	0.0390(12)*
C22	0.3228(4)	0.7003(3)	0.3857(3)	0.0469(13)*
C23	0.3163(4)	0.7825(4)	0.4448(3)	0.0596(16)*
C24	0.2290(5)	0.8464(4)	0.4364(4)	0.0655(16)*
C25	0.1495(4)	0.8292(4)	0.3701(4)	0.0632(15)*
C26	0.1563(4)	0.7462(4)	0.3125(3)	0.0514(14)*
C31	0.0490(4)	0.5857(4)	-0.0612(3)	0.0366(12)*
C32	0.0676(4)	0.6616(3)	-0.1255(3)	0.0482(14)*
C33	0.0032(4)	0.6712(4)	-0.2043(3)	0.0528(15)*
C34	-0.0789(4)	0.6053(4)	-0.2193(3)	0.0552(15)*
C35	-0.0958(4)	0.5277(4)	-0.1581(3)	0.0565(15)*
C36	-0.0319(3)	0.5180(4)	-0.0785(3)	0.0469(13)*
B	0.1665(5)	0.4835(4)	0.1534(3)	0.0419(15)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance
O1	C6	1.421(4)
O1	B	1.454(5)
O2	C8	1.417(4)
O2	B	1.446(6)
N	C7	1.486(4)
N	C9	1.490(4)
N	C10	1.497(5)
N	B	1.739(5)
C1	C2	1.347(5)
C1	B	1.575(6)
C2	C3	1.479(5)
C3	C4	1.314(6)
C3	C5	1.464(6)
C6	C7	1.526(5)
C6	C21	1.520(5)
C8	C9	1.525(5)
C8	C31	1.491(5)
C10	C11	1.516(5)

Atom1	Atom2	Distance
C11	C12	1.368(5)
C11	C16	1.395(5)
C12	C13	1.363(6)
C13	C14	1.358(7)
C14	C15	1.380(6)
C15	C16	1.393(6)
C21	C22	1.376(5)
C21	C26	1.398(6)
C22	C23	1.390(5)
C23	C24	1.385(6)
C24	C25	1.391(6)
C25	C26	1.385(6)
C31	C32	1.390(5)
C31	C36	1.376(5)
C32	C33	1.391(5)
C33	C34	1.365(6)
C34	C35	1.375(6)
C35	C36	1.396(5)

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C6	O1	B	108.7(3)	C12	C13	C14	121.1(5)
C8	O2	B	109.3(3)	C13	C14	C15	119.7(6)
C7	N	C9	113.3(3)	C14	C15	C16	119.5(5)
C7	N	C10	111.6(3)	C11	C16	C15	120.0(5)
C7	N	B	102.4(3)	C6	C21	C22	120.4(4)
C9	N	C10	112.3(3)	C6	C21	C26	119.7(4)
C9	N	B	101.8(3)	C22	C21	C26	119.9(4)
C10	N	B	114.8(3)	C21	C22	C23	121.2(5)
C2	C1	B	123.2(4)	C22	C23	C24	118.6(5)
C1	C2	C3	128.0(4)	C23	C24	C25	121.0(5)
C2	C3	C4	118.8(5)	C24	C25	C26	119.8(5)
C2	C3	C5	117.7(4)	C21	C26	C25	119.6(5)
C4	C3	C5	123.5(5)	C8	C31	C32	119.7(4)
O1	C6	C7	103.7(3)	C8	C31	C36	121.4(4)
O1	C6	C21	111.3(4)	C32	C31	C36	118.8(4)
C7	C6	C21	114.0(4)	C31	C32	C33	120.7(5)
N	C7	C6	104.3(3)	C32	C33	C34	119.9(5)
O2	C8	C9	103.3(3)	C33	C34	C35	120.0(5)
O2	C8	C31	111.7(3)	C34	C35	C36	120.4(5)
C9	C8	C31	113.6(3)	C31	C36	C35	120.1(5)
N	C9	C8	104.1(3)	O1	B	O2	112.2(4)
N	C10	C11	115.0(3)	O1	B	N	100.3(3)
C10	C11	C12	120.1(4)	O1	B	C1	115.0(4)
C10	C11	C16	121.3(4)	O2	B	N	100.5(3)
C12	C11	C16	118.6(4)	O2	B	C1	112.2(4)
C11	C12	C13	121.0(5)	N	B	C1	115.2(4)

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle
B	O1	C6	C7	46.5(4)
B	O1	C6	C21	169.5(4)
C6	O1	B	O2	-135.3(4)
C6	O1	B	N	-29.4(4)
C6	O1	B	C1	94.8(5)
B	O2	C8	C9	46.1(4)
B	O2	C8	C31	168.7(4)
C8	O2	B	O1	77.9(4)
C8	O2	B	N	-27.9(4)
C8	O2	B	C1	-150.8(4)
C9	N	C7	C6	132.2(3)
C10	N	C7	C6	-99.8(4)
B	N	C7	C6	23.4(4)
C7	N	C9	C8	-83.7(4)
C10	N	C9	C8	148.7(3)
B	N	C9	C8	25.5(4)
C7	N	C10	C11	-71.3(4)
C9	N	C10	C11	57.3(4)
B	N	C10	C11	172.9(3)
C7	N	B	O1	2.0(4)
C7	N	B	O2	117.1(3)
C7	N	B	C1	-122.1(4)
C9	N	B	O1	-115.4(4)
C9	N	B	O2	-0.3(4)
C9	N	B	C1	120.5(4)
C10	N	B	O1	123.1(3)
C10	N	B	O2	-121.8(4)
C10	N	B	C1	-1.0(5)
B	C1	C2	C3	175.2(4)
C2	C1	B	O1	13.8(7)
C2	C1	B	O2	-116.0(5)
C2	C1	B	N	129.7(5)
C1	C2	C3	C4	-167.2(5)
C1	C2	C3	C5	11.9(7)
O1	C6	C7	N	-43.1(4)
C21	C6	C7	N	-164.3(4)

Atom1	Atom2	Atom3	Atom4	Angle
O1	C6	C21	C22	148.8(4)
O1	C6	C21	C26	-34.0(5)
C7	C6	C21	C22	-94.4(5)
C7	C6	C21	C26	82.8(5)
O2	C8	C9	N	-44.2(4)
C31	C8	C9	N	-165.4(3)
O2	C8	C31	C32	-178.5(4)
O2	C8	C31	C36	2.5(5)
C9	C8	C31	C32	-62.2(5)
C9	C8	C31	C36	118.9(4)
N	C10	C11	C12	-91.0(5)
N	C10	C11	C16	89.9(5)
C10	C11	C12	C13	176.9(4)
C16	C11	C12	C13	-4.0(7)
C10	C11	C16	C15	-178.3(4)
C12	C11	C16	C15	2.5(7)
C11	C12	C13	C14	2.3(8)
C12	C13	C14	C15	1.0(8)
C13	C14	C15	C16	-2.4(8)
C14	C15	C16	C11	0.6(7)
C6	C21	C22	C23	177.6(4)
C26	C21	C22	C23	0.4(7)
C6	C21	C26	C25	-176.7(4)
C22	C21	C26	C25	0.4(7)
C21	C22	C23	C24	-0.5(7)
C22	C23	C24	C25	-0.2(7)
C23	C24	C25	C26	1.1(7)
C24	C25	C26	C21	-1.2(7)
C8	C31	C32	C33	-176.8(4)
C36	C31	C32	C33	2.2(6)
C8	C31	C36	C35	177.1(4)
C32	C31	C36	C35	-1.8(6)
C31	C32	C33	C34	-0.3(7)
C32	C33	C34	C35	-2.0(7)
C33	C34	C35	C36	2.4(7)
C34	C35	C36	C31	-0.5(7)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.041(2)	0.039(2)	0.0412(19)	-0.0025(16)	0.0081(16)	-0.0060(17)
O2	0.044(2)	0.048(2)	0.0380(18)	0.0068(18)	-0.0039(16)	-0.0110(16)
N	0.032(2)	0.033(2)	0.034(2)	0.0012(18)	-0.0036(17)	0.0042(19)
C1	0.054(4)	0.048(3)	0.034(3)	-0.006(2)	0.001(3)	-0.007(3)
C2	0.036(3)	0.042(3)	0.049(3)	-0.005(3)	-0.008(3)	-0.001(3)
C3	0.041(3)	0.039(3)	0.061(4)	0.009(3)	-0.007(3)	-0.009(3)
C4	0.036(3)	0.062(4)	0.068(4)	0.021(3)	0.005(3)	-0.008(3)
C5	0.109(6)	0.033(3)	0.110(5)	-0.011(3)	0.020(4)	0.006(4)
C6	0.045(3)	0.033(3)	0.035(3)	0.002(2)	-0.002(2)	0.004(3)
C7	0.039(3)	0.039(3)	0.043(3)	-0.007(2)	-0.001(2)	-0.001(2)
C8	0.031(3)	0.041(3)	0.035(3)	-0.003(2)	0.002(2)	-0.004(2)
C9	0.033(3)	0.037(3)	0.033(3)	0.000(2)	0.000(2)	0.005(2)
C10	0.041(3)	0.042(3)	0.042(3)	-0.006(2)	-0.009(2)	0.002(3)
C11	0.033(3)	0.035(3)	0.045(3)	0.000(3)	-0.006(3)	0.007(2)
C12	0.038(3)	0.064(4)	0.051(3)	-0.008(3)	0.000(3)	0.010(3)
C13	0.060(4)	0.106(6)	0.059(4)	0.000(4)	0.009(4)	0.036(4)
C14	0.063(5)	0.091(5)	0.094(5)	0.027(4)	0.033(4)	0.032(4)
C15	0.038(4)	0.045(4)	0.118(5)	-0.006(4)	0.010(4)	-0.003(3)
C16	0.043(3)	0.044(3)	0.069(4)	-0.003(3)	-0.004(3)	0.005(3)
C21	0.050(3)	0.034(3)	0.033(3)	-0.004(2)	0.001(3)	-0.001(3)
C22	0.055(4)	0.053(3)	0.033(3)	0.004(3)	-0.001(3)	0.003(3)
C23	0.069(4)	0.072(4)	0.037(3)	-0.011(3)	0.005(3)	-0.010(3)
C24	0.066(4)	0.064(4)	0.066(4)	-0.016(3)	0.021(3)	-0.016(4)
C25	0.057(4)	0.062(4)	0.071(4)	-0.019(3)	0.013(3)	0.008(3)
C26	0.060(4)	0.054(4)	0.040(3)	-0.010(3)	0.004(3)	0.003(3)
C31	0.039(3)	0.036(3)	0.035(3)	-0.005(2)	0.006(2)	0.005(3)
C32	0.048(4)	0.051(4)	0.046(3)	-0.008(3)	-0.007(3)	-0.003(3)
C33	0.049(4)	0.050(4)	0.060(4)	0.003(3)	-0.004(3)	0.013(3)
C34	0.044(4)	0.079(5)	0.043(3)	-0.006(3)	-0.004(3)	0.016(3)
C35	0.041(3)	0.068(4)	0.060(3)	-0.008(3)	-0.006(3)	-0.007(3)
C36	0.039(3)	0.061(4)	0.040(3)	0.004(3)	0.006(3)	0.002(3)
B	0.046(4)	0.041(4)	0.039(3)	0.001(3)	0.003(3)	-0.008(3)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H1	0.2026	0.3236	0.1394	0.054
H2	0.1343	0.3881	0.3143	0.051
H4A	0.1057	0.1483	0.4089	0.067
H4B	0.0771	0.2677	0.4213	0.067
H5A	0.1987	0.0923	0.2778	0.101
H5B	0.2775	0.1744	0.2340	0.101
H5C	0.1631	0.1530	0.1868	0.101
H6	0.2988	0.5400	0.2843	0.045
H7A	0.2738	0.6830	0.1352	0.048
H7B	0.3842	0.6291	0.1662	0.048
H8	0.1055	0.6430	0.0621	0.043
H9A	0.2461	0.5105	-0.0400	0.041
H9B	0.2694	0.6262	-0.0158	0.041
H10A	0.3469	0.4008	0.0619	0.050
H10B	0.3993	0.4477	0.1537	0.050
H12	0.4163	0.4444	-0.0890	0.061
H13	0.5506	0.5114	-0.1797	0.090
H14	0.6863	0.6055	-0.1144	0.099
H15	0.6904	0.6305	0.0468	0.080
H16	0.5498	0.5683	0.1393	0.062
H22	0.3826	0.6563	0.3905	0.056
H23	0.3706	0.7947	0.4900	0.072
H24	0.2234	0.9027	0.4764	0.079
H25	0.0907	0.8742	0.3643	0.076
H26	0.1015	0.7334	0.2679	0.062
H32	0.1249	0.7075	-0.1155	0.058
H33	0.0164	0.7235	-0.2477	0.063
H34	-0.1244	0.6130	-0.2720	0.066
H35	-0.1512	0.4805	-0.1700	0.068
H36	-0.0444	0.4646	-0.0362	0.056